JUNE 1952

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

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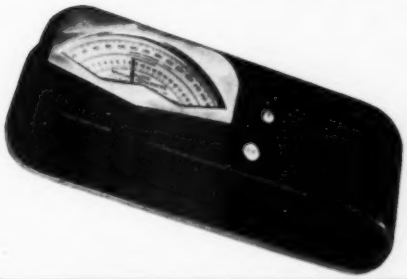

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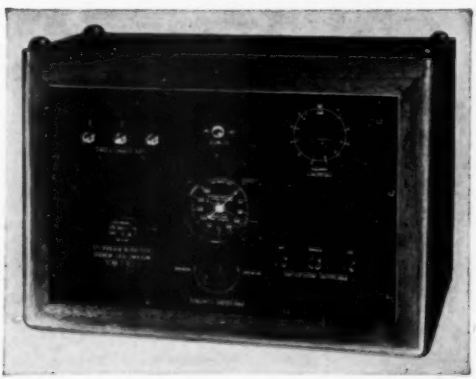

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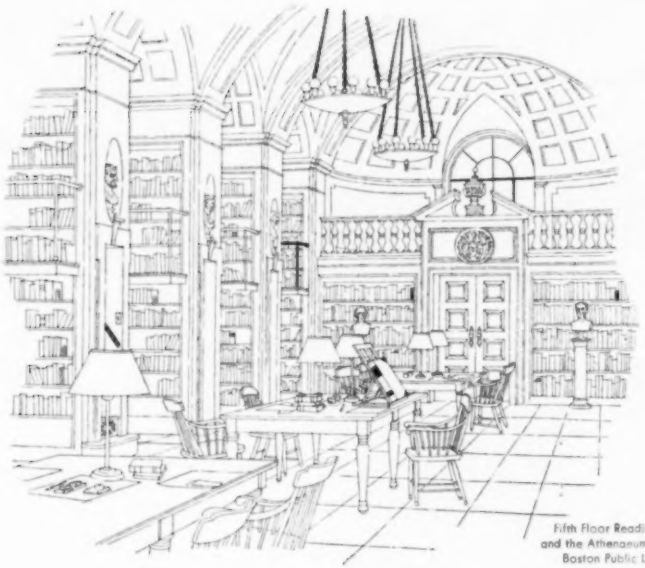

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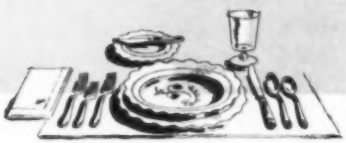

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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 28, NO. 6 JUNE 1952

ADVANCES IN THE TREATMENT OF NON-TUBERCULOUS PULMONARY DISEASE*

ALVAN L. BARACH, HYLAN A. BICKERMAN
and GUSTAV BECK

INTRODUCTION

DURING the preparation of this lecture we were struck by the variety of basic sciences which now seem crucially involved in the therapy of chronic pulmonary diseases commonly encountered by the practitioner of medicine. In the selection made of advances in this field we have included for example, clinical bacteriology, respiratory physiology and the effects of the steroid hormones. The list is by no means inclusive, since limited space and time have necessarily resulted in many omissions of recent progress in allergy, surgery of the chest and circulatory dynamics. Furthermore, we utilized the opportunity of this lecture to summarize the results of current studies in our clinic which seemed pertinent to the treatment of chronic pulmonary disease.

* Read November 9, 1951 at The New York Academy of Medicine in the Friday Afternoon Lecture Series.

From the Department of Medicine, College of Physicians and Surgeons, Columbia University, the Presbyterian Hospital, and the Columbia Division, Goldwater Memorial Hospital, New York.

Advantages and Hazards of Broad-Spectrum Antibiotic Therapy

Among the most interesting of the recent advances in the treatment of non-tuberculous pulmonary disease is the development of antibiotic therapy for chronic bronchial infections. In patients with chronic bronchitis and bronchiectasis, occurring either as separate clinical entities or in association with other chronic respiratory diseases, such as bronchial asthma, pulmonary emphysema and pulmonary fibrosis, the results of appropriate antibiotic treatment are, in some cases, not only a subsidence of the infection itself but a conspicuous clinical improvement in respiratory function, manifested by relief of dyspnea on moderate exertion and disappearance of chronic hypoxia. However, the hazards of treatment aimed at complete arrest, or cure, of chronic bronchitis, or of prolonged and radical decrease of infection in bronchiectasis, have increased as the scope and effectiveness of antibiotic therapy has itself improved.

Although the use of penicillin has been followed in a few patients by infection with gram-negative bacteria (Weinstein[1] and others[2-4]), or, at times, by production of penicillinase[5, 6] which interfered with the effectiveness of penicillin therapy, these infections or reactions may be generally controlled by brief periods of treatment with chloromycetin, terramycin, aureomycin or streptomycin. However, the simultaneous elimination of the ordinary gram-positive and gram-negative bacteria, which is characteristic of the effectiveness of the broad-spectrum antibiotics, is at times followed by infections with B. proteus, B. pyocyaneus and monilia organisms that may develop a unique pathogenicity and invasiveness during periods of marked suppression of growth of the common bacterial flora of the respiratory tract. These new infections, some of which are chronic and at times fatal, have fortunately not occurred in people of relatively good health but in debilitated patients with advanced pulmonary disease who have usually had extensive treatment with broad-spectrum antibiotic drugs.[7, 8] Nevertheless, the incidence of these complications, as well as similar occurrences reported in the therapy of urinary tract disease (to be discussed later) have led to an alteration in point of view in respect to the management of chronic bronchopulmonary infection.

The specific advantage of the newer antibiotics in virus pneumonia

was followed by the demonstration of their value in various types of bronchopulmonary suppuration.[9-19] The simultaneous eradication of gram-positive and the majority of gram-negative organisms from the sputum of patients with pulmonary infections was thought to be, in the main, the explanation for the prompt elimination of pus from the expectoration. It is noteworthy, however, that the broad-spectrum antibiotics are found in small amounts in the bronchial secretions after administration by mouth,[7,8] and that benzyl penicillin does not penetrate into the sputum in effective concentrations after systemic administration. Until recently the only method of producing effective local concentrations in the bronchi and the bronchial secretions has been the administration of penicillin by inhalation. With the discovery and use of the diethylaminoethyl ester of penicillin by Jensen[20,21] and, subsequently its employment by others,[8,22,23] a penicillin preparation for intramuscular injection has been provided which results in effective concentrations of the drug in the sputum, in the lungs, and in the lymph glands as well.

With the present availability of a variety of antibiotics, the question of selection of the drug to be employed, the duration and dosage of treatment poses difficult problems. We have recently appraised the results of a long-term as well as a recent study of antibiotic therapy in chronic bronchopulmonary disease, a summary of which will now be presented.

The broad-spectrum antibiotics are generally preferable to penicillin in the treatment of the exacerbations of bronchopulmonary infection that follow acute upper respiratory disease. Beginning on the third to the fifth day after the onset of an acute coryza or pharyngitis, the use of aureomycin, terramycin or chloromycetin is frequently followed by a prompt control of sinus and bronchial infections. Since these drugs have no effect on the common cold itself, it is unprofitable to employ them at the onset of coryza, since treatment may have to be terminated because of undesirable side-effects at a time when their administration is especially indicated, when the signs of pyogenic bronchial infection become manifest. Although penicillin is therapeutically effective for the control of infections due to gram-positive bacteria, the incidence of allergic reactions to this otherwise non-toxic antibiotic is notably higher than to either aureomycin, terramycin or chloromycetin.

In the treatment of chronic bronchopulmonary infection, however,

in which the aim of therapy is an eradication of chronic bronchitis or a prolonged arrest of the infection in bronchiectasis, penicillin is regarded as the drug of choice despite the possibility of allergic reactions, since the risk involved in long-continued treatment with the broad-spectrum antibiotics is a new infection by organisms not previously pathogenic which may invade the bronchi and lungs during periods of simultaneous eradication of gram-positive and the majority of the ordinary gram-negative bacteria. The basis for the opinions that follow is revealed by the results we have recently assembled, comparing the effect of penicillin with broad-spectrum antibiotics.[7, 8, 23]

Comparison was made of the results of penicillin treatment, mainly by inhalation, in 200 patients with chronic bronchitis and, in addition, either bronchial asthma or pulmonary emphysema to a similar group of forty-six cases treated with the broad-spectrum antibiotics. Significant improvement was recorded in 75 per cent of cases treated with the broad-spectrum drugs and 50 per cent of the penicillin treated series. However, the results of penicillin treatment in 70 cases of *non-asthmatic* chronic bronchitis and in thirty-five cases treated with broad-spectrum antibiotics revealed that significant benefit was obtained in approximately the same proportion of cases, namely 75 per cent. It seemed likely that allergic factors, including an increased incidence of wheezing due to the physical impact of aerosol penicillin, interfered with complete relief of cough and dyspnea in cases with bronchospasm treated with nebulized penicillin.

The use of the systemic route of administration of penicillin, either by mouth or by injection, for patients with asthmatic breathing is now preferable to aerosol penicillin which is of special value in such clinical entities as bronchiectasis, sinusitis, lung abscess and pneumonitis due to penicillin-resistant strains of Staphylococcus aureus. In patients with bronchiectasis the inhalation of aerosol penicillin twice daily, either continuously or in repeated courses, is by far the most effective, practical and inexpensive method of long-term control of advanced bronchial infection.[24-36] In cases of bronchial asthma and bronchiectasis in which systemic administration of benzyl penicillin does not produce the expected improvement, and aerosol penicillin is employed, the previous inhalation of nebulized epinephrine is desirable to prevent, as far as possible, bronchospasm from the local effect of the inhaled penicillin mist.

Although gram-negative bacteria appear in sputum culture following adequate penicillin treatment, demonstrated originally after aerosol therapy,[24] invasion by these organisms has been relatively infrequent in our clinic. In 298 cases of respiratory tract infection reported from our clinic over a period of eight years, the use of streptomycin or the broad-spectrum antibiotics was employed in seventeen instances for the treatment of either Klebsiella pneumoniae infections or to counteract penicillinase production by gram-negative bacteria or resistant Staphylococcus aureus,[37] factors usually responsible for cessation of improvement with penicillin therapy. In four of 298 cases B. proteus was isolated from the sputum after penicillin treatment but without evidence of actual infection. Although monilia organisms grew out on culture at times, especially when streptomycin was added to penicillin treatment, no instance of clinical disease as a result of infection with monilia was encountered. In one patient, who had previously received aerosol penicillin for a long time, the additional administration of streptomycin and sulfadiazine was followed by the appearance of B. proteus on sputum cultures. In this case the eradication of the common gram-negative and gram-positive organisms by combined penicillin, streptomycin and sulfadiazine treatment appeared to be responsible for chronic B. proteus bronchopulmonary infection. Fortunately, courses of chloromycetin and the diethylaminoethyl ester of penicillin have both yielded temporary improvement in this patient, especially prolonged after the use of the new penicillin iodide ester.

In seven of eighty cases of treatment with the broad-spectrum antibiotics, death was apparently due, at least in part, to the subsequent development of infection with such highly resistant strains as B. proteus, B. pyocyaneus and yeast organisms. Of three patients with bronchiectasis who developed B. proteus infection, two revealed B. proteus on sputum culture for a period exceeding six months in each instance.

The danger of development of infections with highly resistant organisms is now recognized by a number of investigators, Finland,[38] Bloomfield,[39] Waisbren,[40] Wheat et al.[41] Although the fatal infections with B. proteus, B. pyocyaneus and yeast organisms that took place in our series were in patients with grave and debilitating diseases, the frequency with which resistant organisms appear on sputum cultures after broad-spectrum antibiotic therapy indicates the possibility of invasion and,

therefore, the prompt termination of antibiotic treatment when B. proteus is grown from the expectoration.

The danger of allergic reactions to penicillin in these cases appears to be less menacing than persistent infection with a more highly resistant organism for which curative treatment is not now available. The use of diethylaminoethyl ester of penicillin resulted in a temporary elimination of gross pus from the sputum in the two patients with chronic B. proteus bronchial infection now under observation, but the organism has not at any time disappeared from sputum cultures. Chloromycetin has also been beneficial in both of these cases. A more extended discussion of this subject is to be presented in a full report of antibiotic therapy in chronic bronchopulmonary disease but it is pertinent to point out at this time that emphasis on simultaneous eradication of gram-negative and gram-positive organisms with a penicillin-streptomycin combination, or with the broad-spectrum antibiotic drugs, is accompanied by more risk than the initial use of penicillin and the subsequent employment of streptomycin, aureomycin, chloromycetin, terramycin for relatively brief periods in order ultimately to augment the effectiveness of long-continued penicillin treatment.

Penicillin is, therefore, used as the mainstay of long-continued treatment, not only to avoid infection with highly resistant organisms but also because infections of the bronchi and lungs are for the most part initially due to gram-positive bacteria. If invasion with the Klebsiella pneumoniae should take place or if penicillinase production interferes with further improvement, either as the result of its elaboration by gram-negative bacteria, or as a result of Staphylococcus aureus resistant organisms,[37] one of the broad-spectrum drugs is employed for a temporary period to restore penicillin sensitiveness. Following a five-day course of chloromycetin, aureomycin or terramycin, generally 2 grams daily, penicillin treatment is resumed with the aim not only of diminishing the amount of pus in the sputum but of reducing, as far as possible, chronic inflammatory swelling of the bronchial wall, which is itself the cause of obstructive dyspnea in many of these cases of bronchopulmonary disease.

In studies now in progress, the employment of the diethylaminoethyl ester of penicillin has appeared to have a special value in bronchopulmonary infection, comparable in some respects to the effective employment of aerosol penicillin.[23] As shown by Jensen[20,21] concentrations of

this drug in the lungs after intramuscular injection are five to ten times higher than that of benzyl penicillin and its presence in the sputum in effective concentrations has also been confirmed by Heathcote[22] as well as by ourselves.[23] Prompt reduction or elimination of pus from the sputum occurred in 75 per cent of fifty patients with chronic bronchitis and bronchiectasis, with a comparable clinical improvement. An illustrative case history of the use of this drug and a broad-spectrum antibiotic (chloromycetin) is presented at the end of this paper.

The Value of Deliberate and Mechanically Induced Coughing in Respiratory Diseases

The second topic selected for discussion is the value of coughing in the elimination of bronchial secretions. Although the cough induced by postural drainage is recognized as beneficial in bronchiectasis, the importance of deliberate coughing in other chronic respiratory diseases is not adequately appreciated. Indeed, it is frequently regarded as harmful and dealt with by cough suppressants. In cases of chronic bronchitis, pulmonary emphysema, pulmonary fibrosis and bronchial asthma, coughing represents a highly effective method of obtaining drainage of mucoid and muco-purulent secretions, especially after bronchodilation has been obtained by inhalation of a bronchodilator aerosol, such as 1 per cent epinephrine, 2.25 per cent racemic epinephrine or 0.5 per cent isopropyl adrenalin. These agents are generally used to terminate bronchospasm in cases of bronchial asthma and pulmonary emphysema but the patients may not cough when dyspnea is relieved by epinephrine inhalations, unless especially instructed to do so, one or two minutes after the inhalation. Coughing is therefore prescribed in order to eliminate mucus that might otherwise be present in the bronchial tubes and result in wheezing and to prevent localized areas of atelectasis and infection.

The improvement recorded in respiratory function tests after inhaling nebulized epinephrine seems to be related at times to the coughing up of mucoid or muco-purulent expectoration. This has become clear in a current study in which the effect of smoking three cigarettes has been studied in cases of bronchial asthma and pulmonary emphysema. In some of these patients in whom coughing due to inhaling cigarette smoke resulted in expectoration of considerable amounts of bronchial secretions, a marked relief of dyspnea took place, with a concomitant

rise in vital capacity and in maximal breathing capacity. The cough in these clinical entities, whether produced by epinephrine or by cigarette smoking, should not be interpreted simply as an irritative phenomenon but must be viewed also in the light of its physiologic use as a factor in drainage. Similarly, when the use of aminophylline and ephedrine is not spontaneously followed by expectoration, if bronchodilation has separated mucus from the bronchial wall, deliberate coughing is recommended. Smoking three cigarettes in succession has also produced increased bronchospasm in some cases, demonstrated by decrease of the vital capacity and maximal breathing capacity, but the point of the present discussion is not to evaluate the harm or the advantage of smoking but to emphasize the functional significance of either a natural or stimulated cough when it is followed by expectoration of mucus and pus from the bronchi.

In a study of physical methods of eliminating bronchial secretions by producing a swift flow of air during expiration, two devices which simulate the human cough have been developed.[42] The first, called a mechancial cough chamber, consisted of a modification of the immobilizing lung chamber used for the treatment of pulmonary tuberculosis. In this apparatus an alternate rise and fall of pressures of 110 mm. above the atmosphere was carried out twenty-five times a minute. Instead of a gradual fall of a previously established positive pressure to that of the atmosphere, a swift opening of a 5-inch valve in the head compartment of the chamber initiated an explosive decompressing effect in which a high volume flow rate of air from the lungs took place during the expiratory cycle. With a collar closed tightly around the neck of the patient a differential pressure of 40 mm. Hg was obtained on the chest wall and abdomen, which not only prevented expansion of the chest during the period of sudden decrease of pressure but also exerted a compressing effect on the thorax and diaphragm which aided the elimination of bronchial secretions.

In the second device a sudden release of pressure after full inflation of the lungs resulted in a swift outflow of air during expiration. This was accomplished with the patient in the conventional tank respirator, the head being in the atmosphere, or by a pressure hood, in which the head of the patient was surrounded. When the tank respirator was employed the negative pressure around the body was gradually increased to 40 mm. Hg and, at the end of the inspiratory cycle, the swift opening

of a 5-inch valve resulted in a rise in pressure to that of the atmosphere in 0.04 seconds. The volume flow rate of air at the start of expiration was found to be equal to that of a moderately vigorous cough, as determined by spirometer recording, and about 75 per cent that of maximally vigorous coughs in normal human subjects.

The kind of ventilation produced by the immobilizing lung chamber, without the use of the cough mechanism, is comfortable and efficient; residence in the chamber has been recently shown to result in the disappearance of orthopnea in many patients with bronchial asthma and two cases of congestive heart failure. The pressure change is similar to the effect of being transported to a 5500 feet altitude and back again 25 times a minute. Patients who have impairment of breathing, either through paralysis or through weakness of the respiratory musculature, may breathe to the extent to which they are able, *without* interference by the alternating pressure. The addition of the cough mechanism to this chamber makes possible its use not only for maintenance of an adequate effortless ventilation but elimination of retained secretions, in patients with infantile paralysis, myasthenia gravis, or atelectasis of the lungs from a variety of causes.

The simpler mechanism has been called exsufflation. The elastic recoil of the lungs and chest wall after previous full inflation results in a higher velocity of air flow during expiration than would have taken place if the lung relaxation pressure were opposed by a gradually decreasing negative tank pressure. The elastic characteristics of the lungs and chest wall have been recently studied by Rahn et al.,[43] Fenn,[44] and Proctor et al.[45] under conditions of variable lung volume during inspiration. The relaxation pressure, which is responsible for expiration, begins to increase rapidly when the lungs are expanded beyond 53 per cent of the vital capacity. Since mechanical inflation of the lungs by increase in negative tank pressure has similar effects to inflation of the lung by pressure applied through a mask over the face, the physiological response in terms of respiration and circulation are quite comparable, as pointed out by Whittenberger et al.[46, 47] and confirmed in studies made in our clinic.[48]

During pressure breathing in normal subjects, the venous pressure is increased approximately 40 per cent of the applied intrapulmonary pressure, the remaining pressure being taken up by the lungs, chest wall and diaphragm; in patients with pulmonary congestion due to heart

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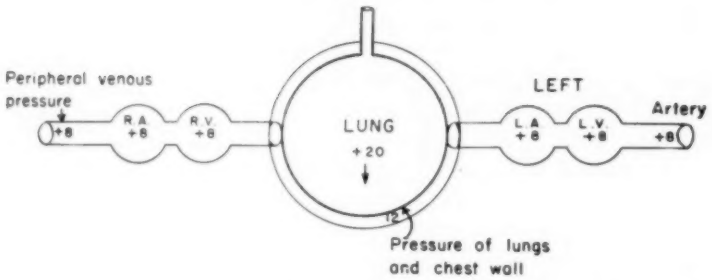


Figure 1: The difference between the applied intra-pulmonary pressure and the venous pressure rise is equivalent to the relaxation pressure of the lungs and surrounding structures. Data from Barach, et al. J. Aviat. Med. 17:290, 1946, reprinted by permission.

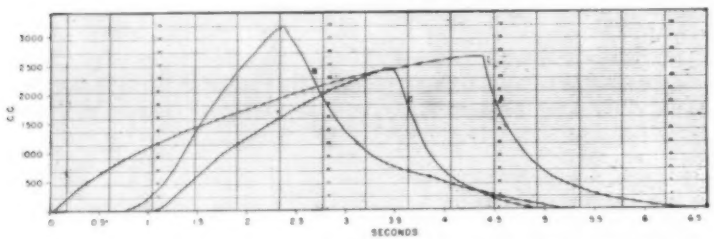


Figure 2: Maximal Expiratory Flow Rate of a Normal Subject (A) During a Natural Cough 3690 cc/sec., (B) During Mechanical Exsufflation 3210 cc/sec., (C) During Swift Manual Compression of Upper Abdomen and Lower Ribs, 3230 cc/sec.

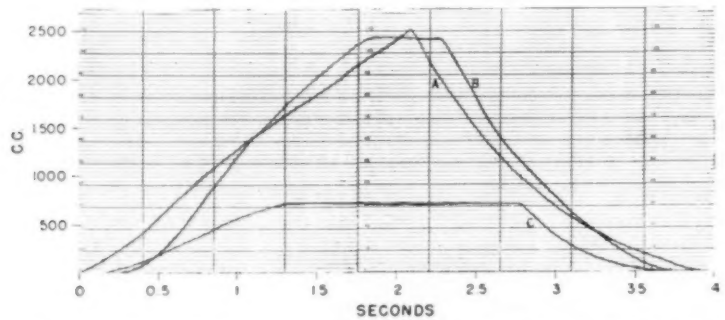


Figure 3: Maximal Expiratory Flow Rates of a Patient with Poliomyelitis: (A) During Mechanical Exsufflation 1915 cc/sec., (B) During Mechanical Exsufflation with Swift Manual Abdominal Compression 2223 cc/sec., (C) During a Natural Cough 1479 cc/sec.

failure, the rise in venous pressure may be 60 to 70 per cent of the applied intrapulmonary pressure, the lung, under these circumstances, being less elastic and acting, to some extent, as a counter-pressure similar to the application of a pressure vest around the thorax.[49,50] From these studies the lung tension responsible for high velocity expiration, which was calculated by subtracting the rise in venous pressure from the applied intrapulmonary pressure, would be dependent on the elasticity of the lungs, the surrounding thoracic structures and the diaphragm.

When inspiration is accomplished by inflating the lungs with pressures of 20 to 40 mm. Hg of water, the pressure available for collapsing the chest in normal individuals may, therefore, vary approximately from 12 to 24 mm. Hg. This response is illustrated in Fig. 1.[50] The flow of air leaving the lungs under these circumstances is at an increased velocity, which may also be used as a measure of lung tension when inflation of the lungs is suddenly terminated.

Measurement of the maximal flow rate of air at the beginning of the expiratory cycle was made by means of a recording spirometer with a high speed drum during a cough of maximal force in a normal subject and during mechanically induced exsufflation. The results in one subject were 4090 cc. during the natural cough and 3580 cc. per second during mechanically induced swift expiration. The flow rates in patients with rigid chests and impairment of lung elasticity were lower than those found in healthy normal subjects, as would be expected from the evidence discussed above. Studies carried out in patients with poliomyelitis, who had a severe degree of impairment of respiratory function and who required the use of the rocking bed the majority of the time, also revealed a less marked maximal flow rate during their natural cough and during mechanical exsufflation. Thus, in one patient the maximal flow rate during the natural cough was 1479 cc. per second, with a tidal volume of 600 cc., and during mechanical exsufflation 1915 cc. per second, with a tidal volume of 2500 cc. When swift manual compression of the abdomen was employed during mechanical exsufflation the maximal flow rate was 2223 cc. per second. A graphic record of these results is illustrated in Fig. 3.

The development of swift manual compression of the abdomen is an extension of its use for elimination of trapped air in patients with pulmonary emphysema. Similar high expiratory flow rates may be

obtained by pressing on the lower ribs and abdomen, as in the prone Schaefer method of artificial respiration, provided the pressure is exerted suddenly rather than gradually. A remarkable increase in air velocity during the expiratory cycle may be produced by an individual trained in the application of pressure with the palms of his hands over the lower ribs and abdomen. The maximum flow rate during a vigorous cough of a normal human subject was found to be 3690 cc. per second, during exsufflation 3210 cc. per second, and after abrupt manual compression of the lower ribs and abdomen 3230 cc. per second. These results, illustrated in Fig. 2, indicate that the maneuver may of itself be of critical value in elimination of bronchial secretions in clinical entities in which retention of secretions results in a threat to respiratory function, provided it can be carried out over an adequate period of time. Mechanical exsufflation appears to be a more practical procedure for long-continued use in patients with bulbar poliomyelitis, myasthenia gravis or atelectasis of the lungs from a variety of causes. However, swift manual compression of the lower thoracic cage and abdomen seemed to be of value when used intermittently in conjunction with physical methods of increasing volume flow rate in expiration.

A physiologic response similar to compression of the thorax may be obtained by negative pressure breathing applied by mask to the respiratory passageway; lowering the intrapulmonary pressure results in a decrease of lung volume comparable to that achieved by an equivalent positive pressure on the chest wall and abdomen. In a patient with pulmonary emphysema a mask pressure of 20 cm. H_2O below the atmosphere was employed at the start of expiration to relieve a serious overinflation of the lungs. The vital capacity of twenty such exhalations under negative pressure was increased from 1000 to 2000 cc., with immediate relief of dyspnea, a reaction which duplicated that previously obtained by manual compression of the lower thoracic cage and upward pressure on the abdomen. The clinical use of sudden application of higher negative pressures at the onset of expiration is being investigated as a method of eliminating bronchial secretions. The physiologic effects of negative pressure breathing on the circulation will be referred to later.

The mechanical cough chamber and the exsufflator device have both been employed in animal experiments in which radiopaque material, thorotrast and mucin, was previously instilled by a bronchoscope into the bronchi of anesthetized dogs. The results of x-rays of the lungs

before and after treatment, compared to untreated controls, indicated that 70 to 80 per cent of the introduced thorotrast was eliminated in one to two hours in the animals tested.[42] Furthermore, the diameter of the bronchi was found to be increased, at the peak of 40 mm. Hg pressure, approximately twice that observed at the start of inspiration, which seemed to facilitate the passage of air beyond the obstructing mucin or mucus in the smaller bronchi. The markedly increased tidal volume of exsufflation appeared to be a favorable factor, in addition to the high expiratory velocity, in aiding elimination of mucin.

The clinical use of mechanically induced high volume flow rates in expiration in forty patients with bronchial asthma and bronchiectasis, twelve patients with poliomyelitis and one case of myasthenia gravis has indicated that elimination of bronchial secretions is aided by both the mechanical cough chamber and the simpler method of exsufflation. The value of these procedures was clearly demonstrated in patients with poliomyelitis in whom an effective cough was absent, and in whom atelectasis and secondary pulmonary infection cleared during treatment. In one patient, reported as Case 5 in the Addendum, atelectasis of the entire left lung had been previously unrelieved by two bronchoscopies. During each treatment with the exsufflator, attached to the tank respirator, mucoid and muco-purulent secretions came into the mouth of the patient, with progressive and complete clearing of the left lung and return of the mediastinum to its normal position.*

ACTH and Cortisone in Bronchial Asthma and Pulmonary Emphysema

The favorable effects of cortisone and ACTH in patients with asthma, reported by Bordley, Harvey, Howard and Newman,[51] Randolph and Rollins,[52,53] Rose[54] and subsequently many other investigators,[55-57] suggested that adrenal steroids blocked the reaction of circulating allergens on tissue cells. In addition, in acute infections, such as pneumococcus pneumonia, Finland[58] reported the disappearance of symptoms without, however, an effect on the positive blood culture. It appeared that the specific steroid neutralized or diminished the reactivity of the tissue cells to toxins, without affecting the micro-organisms or other sources of toxins. Without reviewing the extensive literature

* The treatment of this case was supervised by Dr. H. E. Seanor at Willard Parker Hospital. A more complete clinical report of the value of physical methods of inducing high volume flow rates during expiratory cycle will be presented later.

concerning these effects, as well as the metabolic consequences of cortisone and ACTH, the point may be made that the changes resulting from the continued use clinically of these compounds are similar to those seen in Cushing's syndrome or hyperadrenocorticism.[59]

The clinical results in previous reports indicate that a temporary relief of bronchospasm, partial or complete, takes place in approximately 80 per cent of the cases treated, and this is, in most instances, of 1 to 3 weeks' duration. The complications have included those due to diminished elimination of sodium chloride, hypertension, increased fat, the development of infections such as pulmonary tuberculosis or broncho-pulmonary non-tuberculous infection, pulmonary infarction, gastric ulcer, and psychoneurotic or psychotic states. Glaser[60] estimates that approximately 5 per cent of cases on continued therapy developed psychosis, from observations of a group of approximately 200 patients.

Our impressions of the value of ACTH and cortisone are based on the results of 170 courses administered to seventy patients with bronchial asthma and the bronchospastic type of pulmonary emphysema. Of the total of 170 courses, 100 were followed by complete relief from symptoms, fifty by a partial remission and twenty by no favorable effects. Excluding six cases with a remission of two to twelve months the average duration of improvement in the first 100 courses of therapy studied was seventeen days.

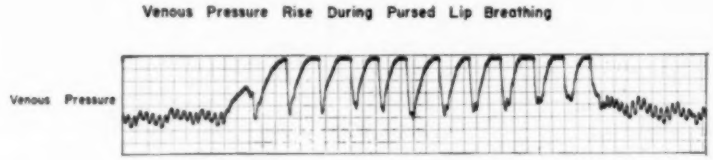
The effect of dosage and selection of cases was later found to be of critical importance in both the initial response and the duration of improvement. With the employment of an increased dosage, such as 600 mg. of ACTH during a five-day period or 1700 mg. of cortisone administered by mouth during the first five days of cortisone administration and 800 to 1000 mg. during the last five days, no incidence of failure of relief of bronchospasm has been encountered in the last fifty courses of therapy. Although one case of pulmonary edema and one case of severe passive pulmonary congestion took place in the earlier treated cases, no unfavorable metabolic effects on the circulation have been observed since the routine employment of potassium chloride and mercuhydrin. Of the series of seventy patients the treatment was judged to be worthwhile in twenty-eight instances, either because of the prolonged nature of the remission or because the improvement obtained was subsequently enhanced by other measures. The ideal indication for administration of these compounds seemed to be intractable broncho-

spasm precipitated by grass or ragweed pollen, in which a self-limiting etiology was plainly evident. The next best-reacting group was that of patients in whom asthma had previously been under reasonably good control but interrupted by an acute respiratory infection. In patients with chronic severe asthma the period of relief was shorter than that accomplished by other measures that produce remissions of intractable bronchospasm.[8]

The development of increased bronchial and pulmonary infection was observed in cases in which purulent expectoration was previously present. In one patient who continued to take cortisone against advice, bilateral pulmonary tuberculosis appeared after two months' treatment. The other non-tuberculous infections were treated by antibiotic therapy but in three cases increased shortness of breath took place because of failure of adequate arrest of the infectious process.

The occurrence of psychotic reaction was not manifested in any case. In our opinion, short intensive courses of treatment appeared to be safer from this point of view, as well as that of the other possible side-effects, than prolonged treatment. A feeling of heightened well being was manifested by the vast majority of patients. In three the euphoria was marked, but not with observable impairment of judgment. In one patient feelings of moderate depression were reported. The presence of severe, uncomfortable stimulation was complained of in only one instance. Within a period of one to two weeks after cessation of treatment these mental effects were absent. It is doubtful that they can be attributed to the relief of symptoms because they occurred to some extent independently of the therapeutic response. The elation which was so commonly observed was different from that induced by dexedrine in that it was accompanied by increased appetite and by a more expansive, cheerful and less tense reaction. Frequently, especially in ambulatory patients, the increased energy resulted in accomplishment of work which subsequent evaluation revealed to be unimpaired from the point of view of the patient's judgment.

When these results are compared to those of prolonged treatment, the impression aroused in us was that little justification is present for maintenance therapy. When repeated courses of therapy are given, the use of cortisone and ACTH alternately seems the better procedure. It must be remembered that many patients with asthma will obtain remission from a variety of measures. We have, for example, observed



	Control	Pursed Lip Breathing	Control
Inspiratory	80.7	92.8	81.5
Expiratory	97.6	159.8	104.5
Mean	88.5	136.2	92.3

Figure 4: The mean rise of venous pressure during pursed lip breathing was 48 mm. H_2O; during the expiratory cycle the rise was 62 mm. H_2O.

three patients who had been on continuous or almost continuous treatment with the adrenal steroids for two months, with inadequate control of asthma, develop a remission after several intravenous injections of Kirk's typhoid vaccine. It would appear undesirable to convert patients with asthma into a state of semi-addiction to ACTH or cortisone in which both metabolic and psychotic effects of a serious nature may take place unless all other measures of remissive therapy had been carefully tried. Potassium chloride, enteric coated, is administered in each case, 0.6 gm. after each meal, with at least one injection of a mercurial diuretic during an intensive course of either ACTH or cortisone. Recently, aluminum hydroxide, 30 cc., has also been routinely prescribed after meals and milk of magnesia at night to combat the rise in gastric acidity.

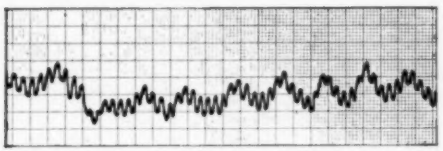
In studies of other forms of respiratory disease temporary improvement has been reported following the use of ACTH and cortisone in pulmonary fibrosis, especially in Boeck's sarcoid,[61] fibrosis with impairment of gaseous diffusion across the alveolar-capillary membrane[62] and the pulmonary lesions due to beryllium poisoning.[63] In some patients with each of these conditions improvement was maintained with continuance of moderate dosages of cortisone.

Advances and Retreats in the Therapy of Non-Tuberculous Pulmonary Disease

The operation of the mechanical cough chamber makes use of a sudden decompression of pressure, namely, a fall of 110 mm. Hg in 0.06 seconds, which results in a swift expansion of gases within the lung

Venous Pressure Fall During Respiration in the Upper One Half of the Respiratory Cycle

Venous Pressure



	Control	Respiration in Inspiratory Position	Control
Inspiratory	84.8	70.4	76.0
Expiratory	107.7	97.5	97.8
Mean	95.2	81.5	85.4

Figure 5: Respiration with the mouth open, with the chest in the inspiratory position, was accompanied by a fall of 14 mm. H_2O in mean venous pressure.

and a high volume flow rate of air at the start of expiration; when this mechanism is combined with an additional compressing pressure on the thorax, muco-purulent secretions are effectively eliminated from the bronchi. If this pressure change is carried out twenty-five times a minute, a pulmonary ventilation adequate for a resuscitation is obtained. In an apparatus decribed by Bloxsom[64] a similar pressure change is induced about one and a half times a minute; under these circumstances the velocity of air movement would be far less than that of normal respiration and no effect on the elimination of bronchial secretions could be anticipated. Furthermore, the pulmonary ventilation achieved by changes in air density is equivalent to less than 10 per cent of that required for a non-breathing subject. Studies by Apgar[65] have indicated that Bloxsom's device did not provide adequate resuscitation in anesthetized dogs.

A few comments on other aspects of physiologic therapy will be included in this discussion. Of the various forms of respiratory exercises used in the treatment of pulmonary emphysema, pursed lip breathing during expiration is one of the simplest to teach patients with this disease. The effect of this procedure has been shown to result not only in a widening of the diameter of the smaller bronchi but in recent studies in a significant elevation of venous pressure. This response,

illustrated in Fig. 4, indicates that blood is retarded from entering the lungs in a manner identical with that imposed by intermittent pressure breathing, and is, in general, equivalent to the mean pressure established in the pulmonary airway. When patients breathe more rapidly with the mouth open, decreasing the pressure in the lungs, the venous pressure falls, as seen in Fig. 5, with the consequence that blood may be more easily aspirated into the lungs, and increase pulmonary congestion if left ventricular failure is present.

In experiments in which subjects were subjected to inhalation of air under negative pressure, a consistent fall in venous pressure was observed. Under conditions of deficient venous return, such as peripheral circulatory failure, use may perhaps be made of intermittent negative pressure breathing to facilitate entrance of blood to the right heart. In right heart failure, in pulmonary emphysema with cor pulmonale, negative pressure breathing during expiration appears to be of value by decreasing right heart strain, through a lowering of the pressure in the pulmonary airway, if left ventricular failure is not also a factor. Under the latter circumstance expiratory pressure breathing, by temporarily retarding the entrance of blood into the right auricle, allows the left ventricle to empty the lungs of blood, and, therefore, effectively counteract pulmonary congestion and edema.

An additional advantage of negative pressure breathing has been demonstrated by a device that allows inspiration to proceed at atmospheric pressure and expiration under a negative pressure of 5 to 20 mm. Hg. This consists of decreasing the functional residual air in a manner comparable to positive pressure applied by the hands to the lower thorax and upper abdomen.

A dramatic relief of dyspnea and cyanosis took place in a patient with pulmonary emphysema to whom this method was applied, comparable to results which have been previously accomplished by a manual elevation of the diaphragm. The vital capacity rose from 770 cc. to 1810 after 160 expirations under negative pressures, and to 2320 cc. after inhalation of 0.3 cc. of 2.25 per cent racemic epinephrine followed by 80 additional expirations under negative pressure. The patient, who had previously been gasping for breath, was able to walk 2120 feet, at the end of which the vital capacity was 1604 cc. Manual elevation of the diaphragm, by pressure applied with the hands to the lower thorax and upper abdomen then resulted in an increase to 1973 cc. (cf. Figs. 6-7).

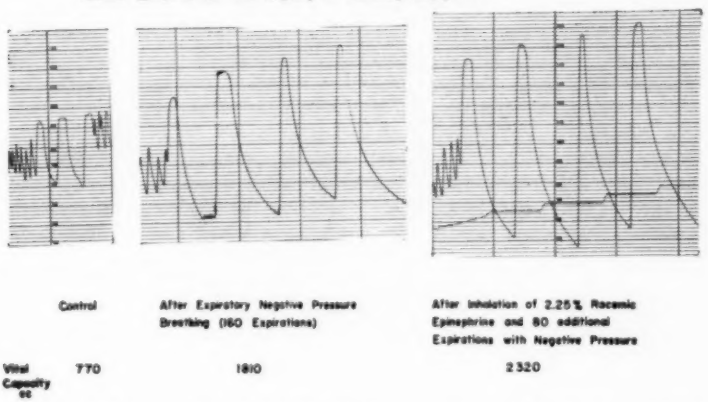


Figure 6: Response of patient with pulmonary emphysema to expiratory negative pressure breathing and inhalation of 2.25 per cent racemic epinephrine.

In a recent paper by Gordon, Motley and Theodos[66] intermittent pressure breathing was reported as a therapeutic measure in patients with advanced fibrosis, pulmonary emphysema and pulmonary tuberculosis. In one such case with marked emphysema, the authors report "marked dyspnea with difficult expectoration followed a period of prolonged rest in bed and residence in an immobilizing chamber; intermittent pressure breathing treatments reduced the dyspnea and facilitated expectoration." Since immobilization of the lungs is not possible in patients with emphysema because of increased bronchiolar resistance, the chest is alternately expanded and compressed in the negative and positive cycles of breathing respectively; the immobilizing lung chamber in these cases results in a variable degree of intermittent pressure breathing.[67] The intermittent pressure breathing treatments mentioned include inhalation of nebulized racemic epinephrine which in itself frequently results in relief of dyspnea in patients with emphysema, due not only to amelioration of bronchospasm but to expectoration of mucus, especially when the patient is asked to take a deep breath and cough after the inhalations. Actually, an inspiratory pressure of 20 cm. H_2O results in a decrease of airway resistance comparable to a similar degree of pulmonary inflation obtained by a deep breath.[68] The bronchial diameter is,

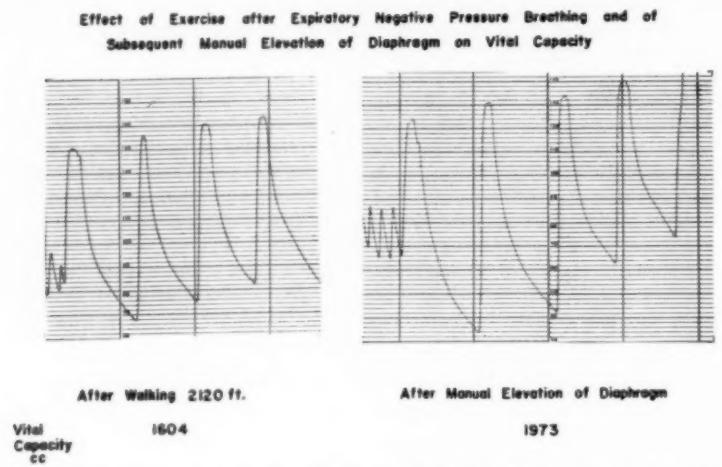

Effect of Exercise after Expiratory Negative Pressure Breathing and of Subsequent Manual Elevation of Diaphragm on Vital Capacity
After Walking 2120 ft.
After Manual Elevation of Diaphragm
Vital Capacity cc
1604
1973

Figure 7: Response of patient with pulmonary emphysema after exercise to manual elevation of diaphragm.

therefore, enlarged in proportion to the degree of lung inflation, whether produced by a natural inspiration or pressure inspiration.

The studies of Gordon et al.[66] do not provide convincing evidence, in our opinion, that the intermittent pressure breathing treatments advocated for patients with advanced fibrosis, pulmonary emphysema and pulmonary tuberculosis have a therapeutic value superior to inhalation of bronchodilator aerosols and effective coughing. Furthermore, as described above, from the point of view of mechanical production of flow rates which simulate the human cough, it has been previously pointed out that very swift falls in expiratory pressure are required to eliminate bronchial secretions.[42]

Among the most valuable of the physical methods recently introduced in our clinic to aid the patient with pulmonary emphysema is the deliberate teaching of diaphragmatic breathing. Even in the presence of a markedly lowered diaphragm, the exclusive use of costal and neck muscle respiration was generally found to be needless; in the majority of cases, some degree of inspiratory descent of the diaphragm is learned through the training program previously described.[8,69,70] The teaching of diaphragmatic breathing requires time and patience on the part of both physician and patient before a habit of abdominal respiration has

been regained. In certain cases, electro-phrenic stimulation or mechanically induced descent of the diaphragm by means of an abdominal resuscitator may be useful to illustrate to the patient that ventilation of the lungs may actually be induced in this way. The patient with this disease usually presents himself with the characteristic upward movement of the chest during inspiration, a habit developed during acute dyspnea and generally continued when the emergency is ended, at the sacrifice of whatever diaphragmatic breathing was formerly employed.

Physiologic measurements which illustrate the clinical improvement in dyspnea after diaphragmatic training are best revealed by x-ray of the lungs and diaphragm on deep inspiration and expiration, as shown in the accompanying roentgenograms (Fig. 8). The maximal breathing capacity, as conventionally carried out, does not mirror the full extent of the clinical gain since instructions to carry out rapid respirations are apt to result in breathing with the accessory muscles of respiration. Comparison of the pulmonary ventilation during inhalation of air and 100 per cent oxygen may more clearly record the advantage of diaphragmatic breathing, since the decrease in the volume of breathing engineered by oxygen is less marked with better alveolar ventilation of the bases of the lungs. The successful use of abdominal belts and pneumoperitoneum is also dependent, for maximal benefit, on the establishment of the practice of diaphragmatic breathing.

A brief discussion of the use of oxygen in pulmonary emphysema seems desirable in order to emphasize that the danger of respiratory acidosis from inhalation of high concentration of oxygen may generally be avoided by understanding the safety and effectiveness of administration of low concentrations of oxygen and a regulated program of oxygen therapy for these cases. Clinical benefit without hazardous depression of pulmonary ventilation may take place from two liters of oxygen per minute administered by nasal catheter, with subsequent gradual increase of the oxygen flow rate. Continuous oxygen therapy, administered in this way, is especially valuable for cases of pulmonary emphysema and cor pulmonale. Respiratory acidosis is prevented by compensatory retention of base and elimination of chlorides, which develop in a progressive manner, with, in addition, excretion of carbon dioxide in higher concentrations in the expired air. In the light of these considerations the solution for the treatment of chronic severe anoxia in pulmonary emphysema is neither ineffective intermittent oxygen therapy nor

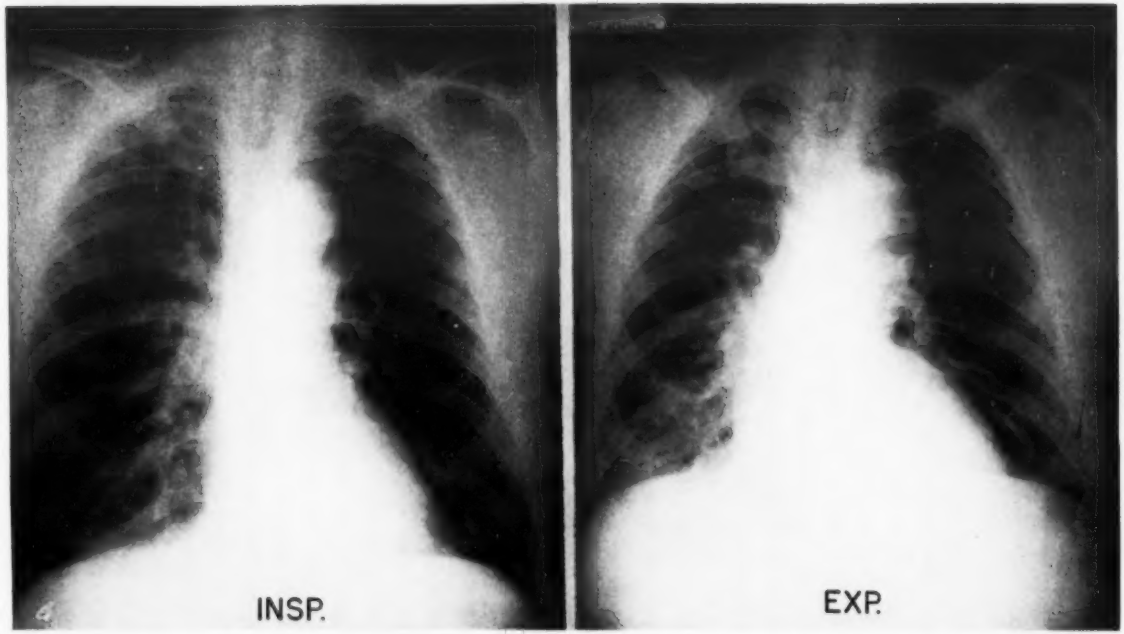


Figure 8: Marked excursion of the diaphragm, 5.5 cm., revealed by films in deep inspiration and expiration, in a patient with pulmonary emphysema who had experienced relief of dyspnea on exertion after three months' training in diaphragmatic breathing.

hazardous high concentrations of oxygen, but rather a graded, continuous, properly controlled program of administration.

Dexter et al.[71] have recently shown that when hypoxia produces an elevated cardiac output, in cases of pulmonary emphysema and cor pulmonale in which the total pulmonary resistance is only moderately elevated, inhalation of oxygen results in return of the cardiac output to normal. In other cases in which lack of oxygen results in a decrease of cardiac output, presumably due to the added load of poor oxygenation on an already overworked heart muscle, inhalation of oxygen is followed by an increase in cardiac output to the expected normal standard. The conclusion of these authors was that administration of oxygen is a specific measure for rapid correction of the circulatory disturbance induced by hypoxia and that it was much more effective than other forms of cardiac therapy.

When respiratory acidosis has taken place as a result of undue depression of the carotid sinus as a consequence of the use of high concentrations of oxygen without preliminary acclimatization, various other measures to counteract the acidosis have recently been tried in a few cases, including intravenous injection of sodium lactate,[72] pneumoperitoneum[73] and mechanical respirators.[74] The mechanical exsufflator described above was of value in a case of pulmonary emphysema with respiratory acidosis since the ventilation was increased in a much more decisive manner than could be accomplished by the routine operation of the tank respirator. The employment of a 40 mm. Hg pressure to inflate the lungs, with the increased expiratory pressure due to mechanical exsufflation, has also been found to result in a marked relief of experimentally induced obstructive dyspnea.[75]

In two patients with pulmonary emphysema in whom dyspnea on exertion was relieved during inhalation of oxygen, an exercise program was instituted with subsequent marked improvement of capacity to exercise without oxygen. A flow of 10 liters per minute of oxygen through a double bent nasal tube was used while the patient strode back and forth across a room. The number of steps walked with oxygen was doubled each day, and the walking without oxygen increased gradually to the point of slight dyspnea. The progressive improvement in ability to walk without dyspnea suggested that a physiologic response similar to a training program in athletes may have been produced. Since the vital capacity did not change significantly as a result of exercise, it

seemed likely that improvement in circulatory function was at least one factor in the benefit obtained. Further studies on physical training with the help of oxygen are in progress in patients with chronic impairment of cardio-respiratory function.

The use of pressure breathing as a clinical therapeutic measure was stimulated in our clinic by observation of a patient with pulmonary emphysema who habitually used pursed lip expiratory breathing on exertion. About the same time Schütz[76] made the following observations: "In the field of respiratory therapy, I use besides the humming exercises of Ludwig Hofbauer the 'whistling expirium.' I had personal favorable experiences during sport activity with whistling expirium which has been advised as a measure for fighting shortness of breath in mountain climbing by Mathias Zdarsky in his book 'Hiking in the Mountains.' Induced by these experiences, I started to use in the treatment of patients suffering from bronchial asthma or emphysema the whistling expirium, i.e., expiring with lips pursed like in whistling as one intended to extinguish the flame of a burning candle from a greater distance. The therapeutic use of this kind of respiratory technique was also stimulated by the observation of Durig that lumbermen expel their air with a whistle together with a stroke of the axe."

It would appear that patients at times inaugurate mechanical aids to respiration and the circulation, too, for which a rational basis is later discovered. The physiologic advantages of grunting and groaning in certain clinical illnesses, such as the expiratory grunt in lobar pneumonia, have been previously mentioned as serving the purpose apparently of preventing pulmonary edema, because of the naturally induced expiratory positive pressure.

Summary

Antibiotic therapy of chronic non-tuberculous pulmonary disease has been discussed on the basis of results of studies of the use of penicillin, the broad-spectrum antibiotics and the diethylaminoethyl ester of penicillin. In the treatment of acute upper respiratory infections, the broad-spectrum antibiotics have the advantage of a prompt control of infection with an infrequent incidence of allergic complications; these drugs have a similar value in the therapy of exacerbations of chronic respiratory infection, such as chronic bronchitis and bronchiectasis, with or without bronchial asthma and pulmonary emphysema.

When the aim of treatment, in cases of chronic bronchitis or bronchiectasis, was a prolonged arrest of chronic infection, penicillin appeared to be preferable as the mainstay of treatment, despite the risk of allergic reactions. The prolonged use of broad-spectrum drugs has been followed by invasion with highly resistant bacteria, which is the special hazard of continued simultaneous elimination of the common gram-positive and gram-negative flora of the respiratory tract in debilitated patients with advanced chronic bronchopulmonary disease. However, limited courses of chloromycetin, aureomycin and terramycin were frequently of marked value, during or after penicillin treatment, when used for the purpose of eliminating gram-negative bacteria or penicillinase production by these organisms.

In favorable cases antibiotic therapy resulted in a remarkable improvement in respiratory function and general health; the disappearance of cyanosis and the alleviation of dyspnea on exertion indicated the importance of decreasing chronic inflammatory swelling of infected bronchi in properly selected patients with chronic bronchopulmonary disease.

The diethylaminoethyl ester of penicillin has the special quality of being concentrated in the lungs and in the sputum in high concentrations after intramuscular injection. The clinical results of its use indicated that a prompt and effective control of infection was frequently achieved in patients with chronic bronchitis and bronchiectasis. This compound appeared to have a unique value in respiratory infections due to gram-positive bacteria.

The importance of deliberate coughing, especially after bronchodilator medication, was found to be a beneficial procedure in patients with bronchial asthma and pulmonary emphysema. A productive cough, induced by inhaling epinephrine aerosols, or at times by cigarette smoke, resulted in improvement in respiratory function in cases in which mucoid or muco-purulent sputum was thereby eliminated.

Methods of simulating the human cough have been developed by mechanically inducing high volume flow rates in expiration. A modification of the equalizing pressure chamber has been employed as well as a simpler exsufflation apparatus attached to the tank respirator. In the latter device the lungs were expanded by a pressure of 40 mm. Hg. and the high velocity expiratory flow rate accomplished by a sudden release of pressure at the height of the inspiratory cycle. Elimination of

bronchial secretions in patients with poliomyelitis was followed by clearing of pulmonary atelectasis. These methods have been used as an aid in the expectoration of mucous plugs and purulent sputum in patients with bronchial asthma and pulmonary emphysema.

A discussion of other forms of physiologically directed therapy included: diaphragmatic respiration, pursed lip respiration, negative pressure breathing, and manual compression of the thorax and abdomen.

The use of cortisone and ACTH in short intensive courses appeared to be preferable to continued therapy in patients with bronchial asthma and the bronchospastic type of pulmonary emphysema, since worthwhile remissions may be achieved in selected cases with little risk of adverse reactions when suitable precautions are followed.

ADDENDUM — ILLUSTRATIVE CASE HISTORIES

Case 1 (Cortisone)

Female, age 48. Family history: Patient's mother and sister have had asthma. Past history: Hay fever as long as she can remember, with a running nose and sneezing, winter and summer. Present illness began three years ago with shortness of breath and a sense of constriction in her chest, noticed first during the summer months, followed that winter by a chronic cough productive of white mucus. During the past two years several disabling attacks of dyspnea and status asthmaticus have taken place for alarmingly long periods of time. During this time there have been twelve hospital admissions for intractable asthma. Skin reactions to timothy and ragweed have been moderately positive with more marked reactions to dust and any bacterial vaccine. A variety of therapeutic procedures were employed, including desensitization therapy, change of climate, inhalational therapy, ether, fever therapy and bronchoscopic aspiration under deep ether. The remissions obtained with the measures outlined have been brief. On the present 13th hospital admission the patient was in severe respiratory distress, cyanotic and harassed. The venous distention of the neck veins was prominent. The neck muscles were prominently employed during inspiration, raising the chest upward and forward. Sibilant and sonorous rales were heard over both lungs with moist rales at the right base. Breath sounds were diminished, especially in the lower lung field. The heart sounds were of fair quality, but the rate was 130. B.P. 130/100. The measures employed on the first two days included intravenous aminophylline, 0.5 gm., administered in 200 cc. of 5 per cent glucose twice daily, nebulized Vaponefrin, 4 gm. of potassium iodide in divided doses, and pressure breathing both by mask and in the tank respirator, a negative pressure of 30 mm. Hg 20 times a minute being employed intermittently for a period of three hours. Although the moist rales in the lungs disappeared following pressure breathing, the severity of bronchospasm was not diminished.

Cortisone was then administered by mouth 100 mg. at 6, 12, 6 and 12, i.e., four times daily, for four days, 75 mg. at six hour intervals for three days, and 50 mg. at six hour intervals for three additional days. The patient was kept in an oxygen tent at a concentration of 50 per cent oxygen during the period when pressure breathing was not administered. The program of treatment included intramuscular injection of mercuhydrin on the second and sixth days of treatment. Potassium chloride, enteric coated, 1.0 gm. three times daily, was given throughout the ten day period. Significant improvement was manifested on the fourth day of treatment, which gradually increased

to the tenth day when a remission of considerable degree was manifested. The continued evolution of mucoid secretions from the bronchi required the use of nebulized Vaponefrin and moderate dosages of aminophylline, viz. 0.2 gm. on arising, at 4 p.m. and 0.3 gm. on retiring. The patient, who has been admittedly "nervous" for many years, noted increased tension as a result of cortisone but also felt well. The control of asthma with the above medication was reasonably good for a period of six weeks when the severity of dyspnea gradually increased. Three similar courses of cortisone by mouth have been given to this patient with partial remissions of three to four weeks' duration.

Comment: In patients in whom asthma was previously under moderately good control, with intractable bronchospasm caused by upper respiratory infection or grass and ragweed pollen, the use of cortisone or ACTH was frequently found to be of substantial value. When pollen-sensitive individuals are tided over the period of pollen in the atmosphere, the succeeding period of relief from asthma may be of long duration and eminently worth while to the patient.

The patient whose history is recited above is an example of an extremely severe chronic asthmatic in whom repeated seizures of status asthmaticus have not been prevented by any of the numerous medical therapies that have been employed. At times she has been gravely ill, with frank pulmonary edema developing apparently as a result of prolonged circulatory strain. Remissions have been obtained with inhalational therapy, iodides and demerol, frequently with bronchoscopic aspiration under deep surgical ether and also by fever therapy initiated by intravenous injection of Kirk's typhoid vaccine. An abundant production of mucoid expectoration, due to, in all probability, extrinsic and intrinsic factors, is continuous. Secondary infection has also taken place which has been treated with prolonged administration of the various antibiotics available. In this patient cortisone therapy was of temporary although dramatic value on four occasions but other measures listed above have also initiated a remission previously.

Case 2 (Chloromycetin)

Male, age 59 years. Following a history of bronchial asthma for thirty-five years prior to hospitalization, the patient developed gradually increasing cough, productive of purulent green mucus for the past four years. At the onset of these symptoms, he also had a cardiac infarct, following which he had periodic cardiac insufficiency. On admission the patient was dyspneic and markedly cyanotic. He breathed 50 per cent oxygen periodically during the examination, a practice that had been initiated two years before. Lung examination revealed widespread sibilant rales, heard in inspiration and expiration, and moist rales over the lower two-thirds of the chest bilaterally. On x-ray, marked accentuation of the bronchovascular markings was noted, consistent with advanced bronchiectasis. Sputum was purulent and yellow, revealing Streptococcus viridans and later Klebsiella pneumoniae on culture. The patient was given the diethylaminoethyl ester penicillin, 1,000,000 units intramuscularly daily for five days with slight reduction in the amount and the purulent quality of the sputum, and persistence of Klebsiella pneumoniae and Strep. viridans on culture. Chloromycetin was then administered in dosages of 3 grams daily for six days with elimination of pus from the sputum, marked relief of cough and dyspnea and disappearance of cyanosis. The in vitro test of the Streptococcus viridans showed it to be sensitive to 1.5 mgs. of chloromycetin. The sputum after treatment showed B. aerogenes on culture and pus cells were absent on smear. The patient was also treated with continuous oxygen therapy by nasal catheter, 6 liters per minute, for one week. The venous pressure fell from 195 mm. H20 to 50 mm. H20 at the end of treatment. Two months later the sputum again became purulent, with Klebsiella pneumoniae on culture. The patient developed asthmatic breathing and cardiac insufficiency. After hospitalization, which included oxygen

therapy, phlebotomy and six days of chloromycetin, sputum again became mucoid, the patient recovered compensation and left the hospital ambulatory, without dyspnea on moderate exertion.

Comment: The response to chloromycetin in this patient with advanced bronchiectasis, bronchial asthma and cardiac insufficiency, was spectacular. Following the disappearance of pus from the sputum, after the administration of chloramphenicol, the patient no longer required oxygen, and was ambulatory, with no cyanosis and with ability to walk five blocks on a level without dyspnea. The patient had previously been treated with digitalis, mercuhydrin, at intervals, and various antibiotic therapies. The fall in venous pressure to a normal level appeared to be associated with the disappearance of anoxia which in turn was the result, at least in part, of adequate antibiotic treatment. The final cultures after chloromycetin therapy revealed B. aerogenes and Streptococcus viridans. The sputum was mucoid with only an occasional pus cell on smear. It is anticipated that in the subsequent management of this patient repeated courses of antibiotic therapy will be required.

The respiratory function tests revealed a sharp increase in ventilatory capacity:

	Before Treatment	*After Antibiotic Therapy*	*Calculated Normal*
Vital capacity cc	1300	2800	3600
Maximal Breathing Capacity cc per min.	12,000	30,000	95,000
Residual air cc		4,100	
Residual air over total capacity per cent		64	35 (highest normal)

Case 3 (Diethylaminoethyl penicillin, diaphragmatic breathing and pneumoperitoneum).

Male, age 52 years. For thirteen years the patient suffered from shortness of breath, cough and purulent expectoration. Two years before admission he had an episode of frank right heart failure with dependent edema, hepatomegaly and distended neck veins. Peripheral edema was improved by digitalization with little relief of dyspnea and cough. For two months prior to admission cortisone and ACTH were administered, with gradual increase in dyspnea, cough and the amount of purulent sputum. For two years prior to entrance to the hospital the patient used oxygen intermittently after exertion. On examination he was seen to be extremely dyspneic with cyanosis evident in the nail beds and frequently interrupted talking by inhaling oxygen from a mask. The thoracic antero-posterior diameter was markedly increased and the chest was very hyper-resonant. Showers of fine moist rales were heard throughout both lungs. Cough with expectoration of green purulent material continued during the examination, later recorded to be 6 to 8 ounces daily. X-rays of the lungs revealed marked bilateral pulmonary fibrosis, and very prominent bronchovascular markings consistent with bronchiectasis, with severe bullous formation in both lungs, especially the right lower lobe.

Treatment was instituted with diethylaminoethyl ester iodide penicillin, one million units being injected intramuscularly for 12 days. At the end of the first week there was a marked reduction in the amount and purulent quality of the sputum with decrease in shortness of breath. Diaphragmatic breathing was taught to the patient, who had formerly employed the customary upward chest movement, employing the intercostals and the accessory neck muscles. Pneumoperitoneum was begun on the eighth day of hospital residence. He was then fitted with an abdominal belt of the Burgess-

Gordon type. Pursed lip breathing on expiration was learned as the patient began to walk in the corridors of the hospital.

At the end of two weeks the improvement in dyspnea was remarkable. Cyanosis was absent and the patient was able to walk up and down the hospital corridor, equivalent to a block, without dyspnea.

The vital capacity was 1790 cc. before treatment and 1940 cc. 23 days after therapy. The predicted vital capacity for this patient was 3680 cc. Maximal breathing capacity increased from 15,450 cc. to 20,350 cc. The expected value was 98,000 cc.

The combined results of diethylaminoethyl penicillin therapy, diaphragmatic breathing, pneumoperitoneum, abdominal support and pursed lip breathing were a conspicuous and radical improvement in well-being and an increased capacity for activity without dyspnea, which had not been present during the previous two years. The expectoration was mucoid instead of muco-purulent. Following discharge the patient went to the theater and on an ocean voyage, a small pneumoperitoneum apparatus having been taken with him. Intermittent oxygen therapy was stopped after two weeks in the hospital and has not been resumed in the follow-up period of eight months since admission.

The relatively slight increase recorded in the tests for ventilatory function fail to reveal the striking clinical improvement in the capacity for exertion without excessive dyspnea. The practice of diaphragmatic breathing during the forced rapid respirations of the maximal breathing capacity test is generally impossible for these patients, and, consequently, ventilation of the lower lobes of the lungs does not take place as it does, in the properly trained subject, during slow walking.

Case 4. Female, age 6. This patient, who suffered from spinal poliomyelitis, had been treated in the tank respirator for three months. She then developed a respiratory infection which was followed by obstruction of the left main bronchus and atelectasis of the entire left lung developed. Bronchoscopy was performed on two occasions during which a small amount of mucus was obtained with no clinical relief or change in the x-ray picture. At this time she was treated with the exsufflator attached to the respirator. An intra-tank negative pressure of 35 mm. Hg was generally used, ten times a minute for one half hour at two hour intervals during the day. During each treatment considerable amounts of mucoid and muco-purulent secretions were brought into the mouth during and after therapy. At the end of five days' treatment the left lung became radio translucent, the mediastinum shifted to its normal position and the patient was clinically and roentgenologically relieved of pulmonary atelectasis. No recurrence took place in the follow-up period of three months.

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RECENT ADVANCES IN TREATMENT OF INOPERABLE CANCER*

The L. Duncan Bulkley Lecture

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Not many years have passed since the time when all that could be said about the treatment of cancer was that the only useful means were surgery, radium and x-rays. Now it seems timely, indeed, that the Bulkley Lecture named for that well-known New York dermatologist who believed in the possibility of a constitutional method of treating cancer, should be devoted this year to a discussion of ways of treating inoperable cancer. The goal of Bulkley and a host of others who have sought a way of curing cancer by constitutional means, has not been reached, nor can it be said to be in sight. Nevertheless, within a relatively short span of years a good deal of progress has been made in effective palliation of some kinds of cancer, and a great impetus has been given to the search along several pathways for clues to the mechanism of cancer formation, and for agents of one kind or another that might destroy the cancer process. That the approach to this problem should be along several pathways rather than from one direction seems necessary, because of the likelihood that there is a lasting verity in what Dr. James Ewing often used to say about cancer, that "it is not one disease, but a thousand different diseases." It seems likely that this concept will hold true even though certain cytochemical or other changes from normal may be found common to all malignant cells. Thus, few of those who have had wide experience with cancer expect that there will ever be found one over-all cure for all of this host of diseases of quite widely varying causes, behaviors, and susceptibilities to therapeutic efforts. It seems much more likely, as is already indicated by some of the experiences in the attempts to treat cancer by whole body agents, that some will respond to one agent or a group of agents, while others will be

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found to be unresponsive to those agents, but perhaps susceptible to other agents of a quite different nature. It may very well turn out, also, that some varieties will prove to be incapable of being favorably affected by any agent.

Nevertheless there is to-day much more to be said for the medical treatment of cancer than could be said two decades ago, or even one decade ago. While one still cannot talk about cure by whole body agents, it is true that in some forms of cancer palliative results that are in some instances dramatic are being achieved. Hence there has come about the realization that the internist plays an important role in the fight against cancer.

Before the advent of large-scale planned efforts to treat inoperable cancer by whole body agents, medical measures had already begun to take an increasingly important part in the treatment of cancer as adjuvants to surgery—in preoperative evaluation of the patient, in preoperative preparation, and in postoperative care. These medical aspects of surgical cases have become so deservedly important that one finds the more advanced surgical departments placing major emphasis on problems which have little or nothing to do with surgical technique in the narrower sense, but which may be considered medical. The important problems of fluid and electrolyte balance, for example, have been studied intensively in several surgical departments. Yet these same problems arise, not only in surgical cases but in the care of the patients ill with forms of cancer too advanced for surgery or inappropriate for surgery, and hence the internist has to concern himself with them, so that now the field of the internist in relation to cancer has become a multiple one: 1) in cooperation with the surgeon to evaluate the patient preoperatively; 2) to help medically in preparing the patient for operation; 3) to aid in the patient's postoperative care and convalescence; and, 4) what particularly concerns us in this presentation, to do what he can with all modern available agents in the attempt to control or palliate the great host of cases of cancer not amenable to direct surgical attack.

These features of the internist's role in the cancer problem are formalized in the table of organization of the medical service of the Memorial Center for Cancer and Allied Diseases. The medical service has three closely coordinated and cooperating segments: 1) general medicine, 2) medical neoplasia and 3) experimental chemotherapy.

The general medical segment administers the examining office, where

all new ambulant clinic patients receive their initial study, and from which they are referred to the appropriate service for further study or treatment. The general medical segment conducts the preoperative evaluation and medical preparation, and the care of complications during the operative and early and later postoperative phases in cooperation with the surgical teams. Since about 60 per cent of patients with cancer present major medical problems these activities comprise a considerable effort.

The medical neoplasia segment of the medical service is occupied with the treatment of non-surgical types of cancer by applicable accepted methods—radiation, chemotherapy or hormones.

The experimental chemotherapy segment which has been active for the past several years, has been formally established as one of the medical services recently, and in its clinical activities, has to do with the trial in humans having cancer, of various new agents, chemical, hormonal, or viral, which in the screening process have shown promise in the laboratory.

Within the limits of this presentation only some of the major aspects of the problem of treatment of inoperable cancer can be discussed. The history of past attempts at non-surgical treatment of cancer is beyond the scope of this presentation.

Resume of Therapeutic Agents

The important currently employed therapeutic agents against inoperable cancer may be roughly classed under the heading of 1) radiation and 2) chemotherapy.

1. Radiation methods cover a wide scope.

   a. Ionizing radiation emitted from an external source, such as an x-ray tube and used to direct a beam of radiation into the body from without. In usual practice energies in the order of from 50,000 volts to 2,000,000 volts are used, depending on the type of lesion and its depth. Treatment ports in a wide range, from a centimeter in diameter, to those that can encompass the entire body, can be used.

Among refinements in the art of external irradiation with x-rays may be mentioned two of current interest: rotation therapy and grid therapy.

In rotation therapy[1] the patient is fixed to a rotating apparatus in such a way that the site of the tumor becomes the axis about which he

rotates, so that the maximum depth dose is delivered to the tumor, while the skin dose is distributed about the circumference of the body.

In grid therapy the rays are screened through a metal grid so that the skin is irradiated directly only through a series of small evenly spaced perforations in checkerboard pattern.

Other external sources that have been used are radium or radon packs, now largely abandoned because of unwieldiness in favor of x-ray therapy. Neutron sources and betatron sources of high energy in the range of many millions of volts are chiefly of experimental value.

b. Sources of ionizing radiation to be inserted within body cavities, such as the nasal passages, the oral passage, the esophagus, bronchus, vagina, cervix, uterine cavity or rectum. Suitable applicators containing radium or radon are devised for these purposes. In certain sites such as the mouth or cervix it has been possible to deliver intracavitary radiation with x-rays through suitably constructed metal cylinders.

c. Interstitial irradiation by means of radium or radioactive cobalt needles or radon seeds implanted within the tumor.

No attempt can be made here to review the voluminous subject matter of treatment of various forms of cancer by radium or roentgen irradiation. The accumulated experience of many years with radiation methods has pretty well defined their indications and limitations; and in the meantime surgical techniques have improved so that there has been a considerable readjustment of attitude towards several types of advanced cancer as regards suitability for radiation therapy versus suitability for palliative surgery. This shift from radiation to surgery has been seen in cancer of the larynx, lung, esophagus, stomach, pancreas, bladder, uterus and rectum, for example.

d. Internal whole body irradiation by radioactive isotopes may be non-selective as in the case of radiosodium used for chronic leukemia, dependence being made entirely on greater sensitivity of the leukemic cells; or partially selective, as in the use of radioactive phosphorus, depending also to a limited degree on selective uptake by the more rapidly proliferating tumor cells; or highly selective, as in the use of radioactive iodine, depending on the marked avidity of functional thyroid cells for iodine, so that the radioactive material becomes concentrated to a high degree in or adjacent to the tumor of thyroid tissue.

2. Chemotherapy may be subdivided into treatment by:

a. Generally toxic chemicals, such as the nitrogen mustards, urethane, and arsenic.

b. Antimetabolites, such as the folic acid antagonists.

c. Hormones, such as androgens, estrogens, ACTH and adrenal cortical hormones.

In a sense chemotherapy and radiation therapy are combined in the use of radiophosphorus and radioiodine, inasmuch as the chemical nature of these radioisotopes leads to delivery of the radioactivity in greater concentration to the target tissues. This is particularly true in the case of radioiodine, but unfortunately only in those cases of cancer of the thyroid in which the cells of the tumor will still pick up iodine.

Aside from the preceding list of agents now regarded as more or less established as effective palliative agents for the treatment of inoperable cancer, certain other means, some old, some new, have been or are being tested. Among these may be mentioned Coley's toxins, bacterial polysaccharides, and particularly the attempts to adapt various viruses so that they become cancerotropic rather than tropic for neural or other vital normal tissues.

Cancer of the Breast

Cancer of the Female Breast:[2-8] The idea of attempting to control cancer of the female breast by endocrine alterations is at least 65 years old, as it was in 1886 that Sir George Beatson[2] recommended removal of the ovaries. Either surgical or x-ray castration may temporarily bring about some palliative effects in decrease of pain, increase in appetite and weight and to a variable extent some objective evidence of regression of the lesions.

The use of synthetic androgens and estrogens in the treatment of advanced breast cancer has now been under intensive study for several years, and in the various reports there is agreement in a general way that certain subjective and objective temporary palliations may be obtained in some cases, although there are considerable discrepancies as to the percentages of cases in which improvement in various features of the disease is reported by different observers.

In general there is agreement that androgen therapy, commonly used in the form of testosterone propionate in a dose of 100 mg. intramuscularly three times a week, gives about the same effect in the

premenopausal as in the postmenopausal group. Androgens seem to give a somewhat greater incidence of relief from pain of osseous metastases, as well as producing variable regression of the primary tumor in the breast, and of soft tissue and visceral metastases, and partial healing and recalcification of osseous metastases. Moreover, androgens may cause a general symptomatic improvement, which in part may be due to improved erythropoiesis. While some observers report that androgens are much more effective in producing objective evidence of improvement in osseous metastases, others have reported that estrogens are of about equal value for the osseous lesions *in the age group* which all agree is appropriate for estrogen therapy, that is, in women well beyond the menopause. The preferred lapse of years following menopause, whether natural or induced, before estrogens are used is ten years.

In women thus well beyond the menopause estrogens may be fairly effective in producing regressions in soft part lesions, such as the primary tumor, and metastases to viscera, skin, and lymph nodes. Estrogens have commonly been given in the form of diethylstilbestrol, 5 mg. three times a day, or ethinyl estradiol (Estinyl) 0.5 to 1 mg. three times a day.

The reported range of elapsed time before improvement begins following hormone therapy varies widely, from a few weeks to several months, but is usually from about two to five months; while the range of duration of improvement also has varied widely, from one month to two years or more, with an average of about half a year.

In some cases, especially those under treatment by testosterone, when the condition of the patient after long administration of the hormone fails to show satisfactory progress, the mere discontinuance of the hormone may be followed by an improvement at least subjectively.

There may be distinctly undesirable side effects of sex hormone therapy. Either androgens or estrogens may cause salt and fluid retention, leading to edema and risk of cardiac failure. The masculinizing effects of androgens, and the gastrointestinal symptoms caused by estrogens may be troublesome. Uterine bleeding may result from the estrogens, either during continued administration or upon withdrawal. It has been reported that uterine bleeding occurring during the continued administration of estrogens may stop if the dose is increased. Especially in patients with osseous metatases there may be an elevation of serum calcium before treatment, and while in most of the cases the

level of calcium will fall after hormone therapy is begun, in some instances there has occurred a dangerous degree of hypercalcemia.

As an almost ultimate step in hormonal control of mammary cancer, bilateral adrenalectomy and maintenance of the patient on cortisone, has been recently tried. This procedure is still experimental, and it is too early to draw conclusions about its results.

Cancer of the Male Breast: For cancer of the male breast orchiectomy may have definite palliative value, as shown by Treves[9] in a study of thirteen cases. He even ventured to propose orchiectomy alone for breast cancer in elderly men, who are poor operative risks, as a much less hazardous procedure than radical mastectomy, and particularly because of long survival of two patients, with primary operable breast cancer. One of these had a local excision of the breast tumor and castration at the age of sixty-four years and was living without evidence of activity of the cancer five years and four months following castration. The other patient, aged eighty-five years, was living four years and five months following treatment by castration alone.

When, in these cases of male breast cancer, the disease became active again, following castration, stilbestrol failed to bring about any palliation.

Cancer of the Prostate[10-15]

That prostatic carcinoma may be dependent upon androgens was strongly suggested by the work of Huggins. For example, Huggins,[10, 11] showed that in dogs in which the prostate was isolated from the bladder, the administration of androgens caused a metaplasia of prostate cells simulating cancer, and the administration of estrogens restored the gland to normal. Moore[13] could find no record of cancer of the prostate in eunuchoids, and in 28 autopsies on men who had eunuchoidism, eunuchism, or pituitary infantilism beginning before the age of 40 he found no evidence of benign prostatic hypertrophy.

It had previously been shown that phosphatase active in *acid* solution is present in the adult prostate, and in metastases of prostatic carcinoma, and may be demonstrated to be well above normal levels in the serum in many cases of prostatic cancer in which the disease has grown through the capsule of the gland or has metastasized. Measurement of *acid* phosphatase in the serum has therefore become a routine in the study of cases of prostatic cancer, although in some cases with met-

astases the level of acid phosphatase may be normal. In fact some observations have indicated a considerable independent variation between tumor activity and levels of acid phosphatase.

Alkaline phosphatase, which may be elevated as a result of liver disease, including metastases in the liver, may otherwise be a useful index of the activity of osteoblastic reparative processes in bone, in cases of prostatic cancer, as well as in other diseases affecting the bones.

From the foregoing facts stem the modern methods of treating inoperable prostatic cancer. First came orchiectomy as a means of removing a source of androgens. Orchiectomy has often produced dramatic results in causing rapid disappearance of pain in bone metastases, disappearance or regression of pulmonary and soft part metastases, together with marked improvement in appetite, weight and strength. A variable degree of healing of the metastases in the bones may occur, and may be foreshadowed by a rise in alkaline phosphatase. The acid phosphatase may fall following orchiectomy.

While such results support the endocrine relationship of cancer of the prostate they are temporarily palliative only, and on the average in about one year relapses occur, and unless there were another means of modifying the hormonal milieu, the patients would succumb to the disease without further effective palliation. It is suspected that the reason for these failures lies in a persistence or an increase of androgens from other sources, a known source being the adrenals. The fact that following orchiectomy the gonadotropins rise to high levels, and that 17-ketosteroids tend to rise above preorchiectomy levels, after an initial fall, may suggest that adrenal androgens increase.

Another obvious means of attempting to influence prostate carcinoma, since it may be dependent at least in part, on androgenic stimulation, is to give estrogens; and since castration, although temporarily effective, is often followed by an increase in gonadotropins and perhaps in 17-ketosteroids, suggesting an increase of adrenal (or other) androgens, the administration of estrogens seems all the more logical. The undesirable effects of estrogens, such as impotence and gynecomastia, seem a small price to pay for relief from the symptoms of prostatic cancer.

That this problem is not a simple one of removal or "neutralization" of androgens is strongly hinted by observations that in a few instances improvement may follow temporarily upon withholding further estro-

gen therapy, or that the administration of testosterone may either cause no apparent stimulation to the cancer, or may even be followed by clinical improvement.

Trials of progesterone have yielded some indication that it may be effective to some degree in palliation of prostatic cancer.

Nesbit and Baum[14] recently reviewed the subject of endocrine control of prostatic carcinoma, making a survey of 1818 cases provided by fourteen cooperators. The series consisted of 947 cases followed for three years, and of 607 cases followed for five years, the latter not as a continuation of the three year study. Survivals were compared with those of 795 untreated cases.

All cases in this series were treated by endocrine modification, that is, by orchiectomy alone, by estrogens alone (the equivalent of from 1-5 mg. a day of Diethylstilbestrol), or by a combination of orchiectomy and estrogens.

They felt that the maximum benefit was best obtained by beginning treatment as soon as the diagnosis was made. The survivals for three and five years were significantly greater in these endocrine treated patients than among others.

If metastases had not yet occurred, the value of orchiectomy alone and of estrogen therapy alone seemed about equal, but a combination of the two produced a greater survival percentage.

If, on the other hand, metastases had occurred, orchiectomy alone seemed more effective than estrogens alone, and the combination of the two methods seemed no more effective on the five year survival percentage than orchiectomy alone. In fact in the five year study they were astonished to find that the survival percentage of patients receiving estrogens alone was not significantly greater than that of the control group. Despite the failure to show statistically greater five year survival percentages in those receiving estrogens alone, when metastases were present, they point out that a large number of such patients did respond dramatically to estrogens alone, and had long remissions, and, furthermore, in the event of relapse after treatment by one method, retreatment by the other method could be of distinct value.

Comparison of the effects of orchiectomy with those of estrogens for relapse that had occurred following use of one of these two methods, indicated no advantage of one over the other; and they suspected that the symptomatic improvement in some instances might be the re-

sult of nursing care and improved nutrition, rather than a true remission of the activity of the cancer.

Finally, the patients who failed to show any response to treatment had survival rates identical to those in the untreated control group. Moreover, 30 per cent of patients with metastases showed no response to orchiectomy or estrogens or both, and this fact was regarded as an indication of a high incidence of independence of androgens. On the other hand it has been suggested that androgens are manufactured by the adrenals.

The reports of induction of primary cancer of the male breast as a result of the use of estrogens may be seriously questioned, as to whether the cancers found in the breast were not actually metastases from the prostatic cancer. Such cancers found in the male breasts have usually been bilateral, and have usually occurred in patients who had widespread metastases to the skeletal system and often as well to the lymph nodes and viscera.

An analysis of six such cases by Campbell and Cummins[15] and their study of their case, including demonstration by histochemical means of acid phosphatase in the cancers found in both breasts of their patient, together with the fact that mammary cancer is constantly negative for acid phosphatase should largely dispel fear of inducing a new cancer in the male breast when treating prostatic cancer with estrogens.

Because of the suspicion that the adrenals may supply androgens, particularly after orchiectomy, and because of the observations that adrenal deficiency, as in Addison's disease, or complete lack of adrenals following bilateral adrenalectomy may be compensated for fairly well by the administration of cortisone, efforts to further the treatment of advanced prostatic carcinoma by means of total adrenalectomy following orchiectomy have been made. Early experiences with this method have indicated distinct improvement in terms of decrease of pain, restoration of ability to be up and about, or even to work, as well as gain in weight. So far, however, there has been no clear cut evidence of lasting objective improvement following bilateral adrenalectomy.

Neither roentgen therapy nor nitrogen mustards have been very successful in the palliative treatment of carcinoma of the prostate.

Cancer of the Lung

The problem of cancer of the lung is almost entirely that of bron-

chogenic carcinoma. Despite remarkable advances in the technique of thoracic surgery, the treatment of bronchogenic carcinoma, if one considers all the cases, is much more than a surgical problem. Many which bear all the signs of operability prove upon exploration to be completely inoperable. A host of others are obviously inoperable by the time a diagnosis is made, either because of wide extent within the thorax or because of distant metastases.

Although it has been almost traditional on the part of thoracic surgeons and some others to state that radiation therapy is of no value in the treatment of bronchogenic carcinoma, the fact remains that definite subjective and objective improvement may be brought about in many instances by well-planned adequate roentgen irradiation, more particularly in the alleviation of the disease within the chest, than in the palliation of metastatic lesions in bones or viscera. Decrease of pain, cough and hemoptysis, gain in weight and strength may be marked signs of improvement in a considerable number. For most cases million volt therapy is preferable to ordinary high voltage, because of better depth dose, less reaction in the skin, and less radiation sickness. Objective evidence of shrinkage or even marked regression of the tumor is seen in a few.

Cahan[16] has devised an ingenious double use of implantation of radon seeds at the time of surgical exploration of certain inoperable but not too extensive intrathoracic malignant tumors, using the seeds both as radiopaque markers of the site to which roentgen therapy is to be directed, and as sources of radiation within the tumor.

There are certain highly aggressive anaplastic or oat-cell bronchogenic carcinomas which may produce bulky or widely infiltrating tumors in the lung and mediastinum, accompanied by marked thoracic symptoms, and which may not respond well to radiation, and are totally inoperable. About six years ago it was discovered that nitrogen mustard might have a rapid though transitory and incomplete effect in relieving symptoms in such cases, and this observation led to more extensive trial of nitrogen mustard (HN2) on bronchogenic carcinoma, either alone, or in combination with roentgen therapy.[17] One advantage of HN2 is seen in those cases with marked mediastinal block. They are usually considered hazardous for roentgen therapy, and therefore in treating them with roentgen rays, the early doses are best kept small. HN2 has not seemed to carry risk of inducing an edema in a blocked

mediastinum, but rather, tends to relieve the symptoms fairly rapidly. It has even seemed that to some extent the preliminary injection of HN2 served somewhat to protect the patient from risk of an asphyxial reaction following the immediate application of the first roentgen treatments to the mediastinal region.

While the palliation of inoperable cancer of the lung that may result from the intravenous injection of HN2 may be all too brief, it may in some cases be of sufficient degree to be well worth while. A report by Karnofsky et al in 1948[17] stated that 74 per cent of thirty-five patients so treated showed some clinical improvement. In some cases such objective changes as partial regression of pulmonary and metastatic lesions, and absorption of pleural effusions were noted.

To what extent the addition of roentgen therapy immediately following HN2 may contribute to palliation in those cases that would obtain definite palliation from HN2 alone is not clear. On the other hand in the more slowly progressing bronchogenic carcinomas, which may show some response to roentgen therapy, it is not clear that there is any advantage in giving a preliminary course of HN2. Yet if the disease is widely disseminated HN2 may offer some over-all palliation quickly, that would be difficult to obtain by roentgen therapy.

In the treatment of persistent pleural effusion complicating bronchogenic carcinoma or other neoplastic disease the intrapleural injection of HN2 has in some cases had a decided and occasionally a prolonged beneficial effect in drying up the effusion.

Studies are currently in progress on the effects of radioactive gold for pleural as well as peritoneal effusions associated with cancer.[18]

Cancer of the Thyroid

Because of the long known avidity of thyroid cells for iodine, it was naturally hoped, when radioactive iodine became available, that by means of this agent, it might be possible to deliver such a dose of radiation within a thyroid cancer as to lead to its destruction. Unfortunately, experience of investigators in this field has shown that less than 50 per cent of thyroid cancers concentrate demonstrable amounts of I^{131}. The papillary carcinomas, which in most clinics comprise about half of all the thyroid cancers, show a relatively poor incidence of demonstrable up-take of I^{131}, about 30 per cent. The more malignant forms, giant and spindle cell, and anaplastic may show no detectible concentration of

I^{131}. Even those thyroid cancers which still retain some function in terms of avidity for iodine, fail to concentrate as much I^{131} as the adjacent normal thyroid tissue. There is also great natural variation between various metastases in their avidity for iodine.

Hence, one of the cardinal limitations of the treatment of inoperable thyroid cancer is its relative to absolute lack of ability to pick up radioiodine, either in the primary tumor or in its metastases. Rawson[19] has recently reported that in a study of 146 patients bearing cancer of the thyroid it was desirable and possible to administer therapeutic doses of I^{131} in twenty; that by observing certain criteria, effective and relatively safe amounts were given to sixteen; and that objective evidence of improvement, shown by histologic or x-ray evidence of destruction of tumor was obtained in ten patients.

Fortunately for the possibility of palliation of metastatic thyroid cancer, certain procedures may induce the metastases to acquire an increased avidity for iodine. Total surgical removal of the thyroid is one of these procedures. Rawson reports that in thirty-five patients whose normal thyroids had been completely removed, a significant increase in function of the metastatic lesions developed in twenty-one; but in only two of these was there enough increased avidity for I^{131} to justify treatment by I^{131}.

Another procedure for eliminating the competition of the remaining normal thyroid gland for I^{131} is to give a large so-called thyroidectomizing dose of I^{131}.

Following surgical removal of the thyroid gland or the destruction of the remaining normal thyroid by I^{131}, the avidity of the metastases for I^{131} may be enhanced by giving thyroid stimulating hormone of the pituitary (TSH), or by prolonged administration of thiouracil. Rawson reports that the administration of thiouracil in large doses for several months to previously totally thyroidectomized patients causes a maximum pickup of I^{131} in about 70 per cent of cases. He recommends not giving therapeutic doses of I^{131} until the avidity of the metastases for iodine has become great enough to keep the forty-eight hour urinary elimination of a tracer dose of I^{131} down to 30 per cent or less. Further, in order to keep within safe limits of effects on the blood and blood forming tissues, Rawson recommends that the dose of total body irradiation, calculated from daily determinations of blood levels of circulating I^{131} following a tracer dose, should not exceed 500 r e p (roent-

gen equivalents physical).

Despite its limitations, I^{131} has in some instances produced remarkable palliative effects. Metastases to the lungs may disappear or decrease markedly, and pain caused by lesions in bones may be relieved, and occasionally objective evidence of healing or partial healing of metastases may be found. As yet no evidence of curability of disseminated thyroid cancer by means of radioiodine has appeared.

Lymphomas and Leukemia

Aside from those forms of cancer amenable to some degree of control by hormonal agents, namely cancer of the breast and cancer of the prostate, perhaps the most striking examples of effective palliation of non-surgical types of cancer are seen in the malignant lymphomas and the leukemias.[20,31] In this broad category of diseases the cases as a rule present various measurable features, such as lymph nodes, enlarged livers and spleens, roentgenographic evidences of the disease, blood counts, marrow specimens, fever, etc. These measurable features, together with the more or less common sensitivity of these diseases to various therapeutic agents, has led to their taking a more prominent position in cancerology, as prime test objects for the trials of many different kinds of constitutional therapeutic agents. Because of their sensitivity to various agents, the result has been that for their treatment we now have a considerably better stocked medicine chest than was the case a little over a decade ago, when x-ray therapy and supportive measures comprised practically the whole extent of our weapons against them. As is true in general of non-surgical therapeutic agents for cancer, one finds that among the lymphomas and leukemias the various diseases respond differently to each agent, and some forms respond but little if at all.

Within the scope of this presentation only bare outlines of the therapy of malignant lymphomas and leukemias can be sketched. The details of their treatment are extremely complex, since all of the diseases embraced in this general category may affect any structure or function of the body. Yet the general approach to the problem of their treatment may be thought of as relatively simple, in this way: there seems now good reason to believe that Hodgkin's disease and lymphosarcoma, in many instances, begin in a single focus, and that their spread to produce the generalized forms takes place from that initial focus, whether

spread be slow or rapid. The long survivals, without evidence of recurrence or spread, of some patients whose localized malignant lymphoma was recognized and treated early, bear witness to this concept. There are some clinicians who do not accept this concept, and think of Hodgkin's disease and lymphosarcoma as invariably systemic diseases of multiple foci of origin. One must admit, also, the inadequacy of our methods of judging the full extent of malignant lymphoma in the individual patient, or its capacity to spread more rapidly than average. Nevertheless, observation of the course of these cases seems to justify planning their treatment on the basis of the concept of spread from an initial focus.

On this same premise, the approach to the new case of Hodgkin's disease or lymphosarcoma is with the question uppermost as to the extent of the disease. If it is still localized to one region, aggressive local treatment is advocated, by means of roentgen therapy, or in suitable cases even the aid of radical surgery is enlisted.

If, in a case of Hodgkin's disease or lymphosarcoma, spread has begun, but the disease is still apparently relatively regionally limited, and there is no evidence of greater generalization, fairly aggressive local roentgen therapy may still have a chance to bring about long control. In such a situation, with the even greater difficulty of being certain of the actual extent of the disease, the value of combined therapy with nitrogen mustard or TEM may be worth considering.

If the case is one of truly generalized malignant lymphoma, or of plasma cell myeloma, or leukemia, then one has the problem of trying to choose that agent, or that combination of agents that may promise the best palliation for the longest possible time.

The need for early diagnosis is more and more apparent. The concept of unicentric origin of Hodgkin's disease and lymphosarcoma, and the experience of those who have witnessed long control, without spread, of early localized malignant lymphomas, lead naturally to a wish for earliest possible recognition and aggressive treatment of such cases. Even in the leukemias, never diagnosable until they are generalized processes, the results from the newer therapeutic agents in some cases, lead to the hope that some day these diseases may be reversible.

Better palliation for all the diseases in the general category of lymphomas and leukemias follows naturally from greater familiarity with all the lesions they may produce. For example in the malignant lym-

phomas, recognition of the deep and more obscure lesions such as those of the gastrointestinal tract, the osseous system, the central nervous system and the respiratory tract—lesions which may be far more significant for morbidity and mortality than the conventionally thought of lymph nodes, spleen, et cetera—permits more precise treatment resulting in better palliation.

Even in the use of conventional x-ray therapy for malignant lymphomas, attention to accuracy in size and location of treatment portals, avoiding unnecessary body doses, can be rewarding in terms of better tolerance to courses of irradiation and better local effects on the lesions treated.

Supervoltage x-rays in the order of 1 to 2 million volts have certain advantages for some deep lesions by reason of less relative damage to the skin, and less radiation sickness for comparable depth doses.

The increased five year survival rates of successive but overlapping series of cases of Hodgkin's disease and lymphosarcoma treated almost entirely by external radiation and supportive measures suggests that increased experience with those diseases and hence increased precision of treatment led to better results. It seems certain that any greater accrual of earlier cases for which one might expect an increased five year survival was balanced during the years by a greater accrual of advanced problem cases.

In Hodgkin's disease our five year survival rates[21] for successive series of cases, 1918 to 1935, 1930 to 1940, and 1930 to 1943, numbering 265, 283 and 471 cases respectively, have gone up from 17.7 per cent, to 20.5 per cent, and to 23.6 per cent.

In lymphosarcoma[22] the five year survival rates for successive series 1918 to 1933, and 1930 to 1940, numbering 132 and 308 cases respectively went up from 15.9 per cent to 26.3 per cent.

In contrast to only a little over a decade ago, when essentially for the treatment of lymphomas and leukemias we were limited to radiation, arsenic, and supportive measures, we have to-day a range of therapeutic agents, from which a choice may be made, depending on the type of case and extent and stage of the disease. These newer agents are the radioactive isotopes, particularly P^{32}, the nitrogen mustards, nitrogen mustard-like compounds, such as tri-ethylene melamine, urethane, the folic acid antagonists, and hormonal agents such as ACTH and cortisone. It is likely that out of the intensive investigations now

in progress several other agents, some allied to these, and some quite different in nature, will emerge as useful additions to the therapeutic spectrum.

Of the radioactive isotopes tried for lymphomas and leukemias radiophosphorus (P^{32}) is the one that has been most widely used. Among others that have been used are radiosodium (Na^{24}), radiomanganese (Mn^{52}), radiogold (Au^{198}), and radioarsenic (As^{74}). At first, because of certain properties of radiophosphorus it was hoped that it would be almost an ideal treatment for leukemia. These properties are its short half-life of 14.3 days, its emission only of beta rays, penetrating an average of only 2 to 3 millimeters of tissue; and its selective uptake by rapidly growing cells that have a greater turnover of phosphorus. It was soon found in practice that the differential uptake was not of a sufficient order of magnitude to be destructive of leukemic cells alone; and, of course, some of the normal cells, particularly those in the marrow concerned with hematopoiesis not only pick up radiophosphorus themselves but are subjected to bombardment by the beta rays emanating from neighboring leukemic cells. Thus the marrow is one of the great limiting factors in the usefulness of P^{32}, as it would be with any other form of whole body irradiation, and severe pancytopenia can result from overdosage. Hence, in practice, in the treatment of chronic lesions with P^{32}, one is depending more upon a differential in sensitivity to radiation on the part of the leukemic cells, than upon a differential absorption ratio. The circumstances are far different from those existing when radioiodine is given to thyroid tissue having an avidity for iodine.

Nevertheless, radiophosphorus has been one of the useful agents for the treatment of chronic myeloid and chronic lymphatic leukemia, and polycythemia vera. It is administered orally or intravenously in a dose of about 75 to 100 microcuries per kilogram of body weight, either as a single dose or in divided daily doses. Only in very radiosensitive cases of generalized lymphosarcoma would the use of P^{32} be justified. There is general agreement that it seldom benefits a case of Hodgkin's disease, mycosis fungoides, or plasma cell myeloma. The acute leukemias do not respond well to P^{32}, as might be expected from their well-known poor response, in fact their risk of being made worse, by any form of radiation in any considerable amount.

The nitrogen mustard methyl bis (beta-chloro ethyl) amine hydro-

chloride (HN2) was declassified in 1946 and has come into wide usage since then. It is a general cell poison, its effects on the more rapidly proliferating cells, particularly those of the lymphoid system and blood-forming organs being unlike those of other chemicals, and comparable to those of radiation. Hence it is sometimes called a radiomimetic drug. In excessive dosage it can severely damage the marrow and produce a fatal total marrow aplasia. It is injected intravenously in saline solution equalling 1 milligram per cc., and is usually given daily in a dose of 0.1 to 0.2 milligrams per kilogram of body weight to a total of 0.4 to 0.5 milligrams per kilogram. The single lethal dose is estimated at about 1.0 milligram per kilogram of body weight. A very slight extravasation of HN2 can produce a severe local reaction in the tissue. Nausea and vomiting nearly always occur within a few hours after injection of HN2.

Experience with HN2 has shown that the disease for which it is most useful is Hodgkin's disease, that is generalized and producing constitutional symptoms. In such a case rapid "detoxification" of the patient may occur, with subsidence of fever, sweats and usually to a less extent, of itching. Partial to marked regression of nodal masses or infiltrations may result. Osseous lesions do not usually respond well. The adequacy of the dose of HN2 may be estimated to some extent by the degree of leukopenia that usually reaches its maximum in seven to fourteen days. If the patient is leukopenic before treatment extra caution in dosage is advisable, unless the marrow shows adequate cellularity.

As with other new drugs that become popular there is a tendency to use HN2 indiscriminately. There would seem to be little reason for its use in a case of Hodgkin's disease localized to one region. Such a case is better treated by local roentgen irradiation.

There are many disappointments in the use of HN2, even in Hodgkin's disease. With few exceptions the remissions obtained by HN2 last only a few months.

HN2 may be a useful agent for some generalized cases of lymphosarcoma and reticulum cell sarcoma and for chronic leukemia, and has shown good results also in polycythemia vera. It has not produced good results in acute leukemia.

The same range of therapeutic usefulness applies to the recently introduced nitrogen mustard-like compound tri-ethylene melamine (TEM).[27] It may be given intravenously, usually in doses of 2 to 3

milligrams repeated the next day. A total dose of 8 or 9 milligrams within the first week or ten days should not be exceeded. Of advantage is the fact that it can be tolerated and be effective when given orally on a fasting stomach, usually in doses of from 2.5 to 5 milligrams a day, not to exceed 10 to 15 milligrams in any one course. It is therefore more convenient for ambulant patients and for trials of maintenance therapy. Like HN2 it may be severely depressant to the marrow.

The antifolics such as Aminopterin and Amethopterin have revolutionized the treatment of acute leukemias in children, particularly since ACTH and cortisone have become available. Whereas formerly the occurrence of remissions spontaneously in acute leukemia of children or young adults, or of remissions occurring under what little treatment could be given prior to the advent of antifolics, was only of the order of 9 per cent at the most,[31] it is now possible with antifolics to obtain remission in as many as 32 per cent in children, and the average duration of survival has increased from twenty weeks to forty-two weeks.[20] If a child attains one remission from Amethopterin, nearly always a second remission can be induced by the same drug. Furthermore, if it appears that the leukemic cells have become resistant to Amethopterin, the use of ACTH or cortisone may bring about another remission, and in occasional instances the patient then seems to have regained sensitivity to Amethopterin. Remissions may be induced initially more rapidly by steroid therapy, and in from 50 to 70 per cent of children.

The great disadvantage of treatment with the antagonists to folic acid is their toxicity. Toxicity is usually first made known by sores in the oral mucous membrane, and may be accompanied by gastrointestinal disturbances such as anorexia, nausea, cramps, and vomiting. Other signs of toxicity may be diarrhea, intestinal ulceration and bleeding, pancytopenia, petechiae and hemorrhagic tendency, skin rashes, and increased susceptibility to infection. Another disadvantage of the folic acid antagonists is their slowness of action. The steroid treatment may bring a response more quickly.

Disadvantages of therapy with ACTH and cortisone are the metabolic disturbances that may be induced, such as retention of sodium and water, alkalosis, hypokalemia, diabetes mellitus, hypertension, moon facies, muscle wasting and, in short, a change to a picture of Cushing's syndrome.

Lymphosarcoma and reticulum cell sarcoma in children may show

marked responses in some cases to folic acid antagonists. The treatment of adults for any form of malignant lymphoma or leukemia with folic acid antagonists has usually been much less effective than treatment by other means.

While ACTH or cortisone may cause some temporary partial remission in chronic lymphatic leukemia, lymphosarcoma, reticulum cell sarcoma, certain acute leukemias, and plasma cell myeloma in adults, the results on the whole in terms of long salvage are not impressive, although individual cases may show some rather dramatic responses for varying periods. Chronic myeloid leukemia and the myelomonocytoid form of acute or subacute leukemia in adults have not responded well to ACTH or cortisone.

Cortisone may seem to be of value at times for the patients with advanced malignant lymphoma, who have depression of all formed elements of the blood and who do not seem particularly suitable for any of the other forms of treatment. The administration of cortisone to such patients may give them a sense of well-being, improve their appetite, and may seem at times to stimulate the marrow somewhat to produce a better blood picture.

An acquired hemolytic anemia may develop in cases of malignant lymphoma and leukemia. In some such instances a course of ACTH or cortisone may in some way alter the conditions so that the need for transfusions may become greatly decreased or temporarily abolished.

Testosterone may be useful in some cases for its anabolic effect and tendency to improve erythropoiesis.

Urethane has received considerable attention as an agent for the treatment of certain diseases in the lymphoma-leukemia group, particularly chronic leukemias and plasma cell myeloma. Its effects are rather unreliable, and few patients will tolerate doses much above 3 grams a day, without nausea and vomiting. If the patient can tolerate urethane, it may furnish a convenient method of oral medication for chronic leukemia, particularly the myeloid form; and Rundles and others[28-30] have achieved both symptomatic and objective evidence of improvement in some cases of plasma cell myeloma. Urethane is capable of producing severe bone marrow depression or aplasia.

The effects of nitrogen mustard on some sensitive tumors and the resemblance of its tissue damaging effects to those of radiation led Klopp[32, 33] to attempt to treat certain local sites involved by cancer with

nitrogen mustard injected into the artery supplying the affected site. By fractionating the dose of nitrogen mustard and by occluding the venous return from the injected site it has been found that patients can tolerate larger doses of the drug than if it were injected intravenously, and a much more intense local tissue reaction can be produced. Gross and microscopic evidence of regression of tumors indicates a selective action on neoplastic tissue.

Bierman[34] has demonstrated the possibility of intra-arterial catheterization of various sites, including liver, spleen, stomach, kidney and diaphragm. Work has been in progress, in attempting by this means to deliver nitrogen mustard to the arterial supply of the liver, to pelvic organs, and to other sites. This method is accompanied by the distinct hazard of causing arterial thrombosis, and hemiplegia has occurred in several patients following manipulation of intra-arterial catheters.

In this review of efforts to treat inoperable cancer emphasis has been placed on six major fields in which there have been some fairly common successes in palliation, although admittedly far from consistently satisfactory long term results. These fields are: 1) carcinoma of the breast and 2) carcinoma of the prostate, treated by sex hormones, 3) carcinoma of the thyroid, treated by radioiodine, 4) the lymphomas and leukemias, treated by radiation externally, or internally by radioactive isotopes, steroids, or antifolic compounds, 5) carcinoma of the lung, treated by nitrogen mustard and radiation, and 6) the heterogeneous field of cancers considered suitable for radiation therapy rather than surgery.

It seems possible that some of the efforts that were merely mentioned, such as trying to induce viruses to become specifically cancerotropic, or the search for cancericidal chemical compounds, or bacterial or other toxins, or further studies of endocrines may before long produce further advances in our ability to effect some control of inoperable cancer.

While the goal of curative constitutional treatment of cancer still seems far away, the progress that has been made in several areas in partial and temporary control amply justifies persistent and intensified efforts to discover the fundamental abnormality or abnormalities that produce cancer, in hopes that then those deviations from normal may be correctible, and that either by means of such corrections, if possible, or by means of some agent or agents yet to be discovered, cancer may

be made to disappear completely.

Doctor Bulkley compared cancer to a mutiny of cells. Whether removal of the cause or causes of mutiny is possible, or will result in a return to orderly ranks, or whether annihilation of the mutineers is necessary, or possible without too much damage to the orderly economy, remains to be discovered.

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NOTICE

THE FRIDAY AFTERNOON LECTURE SERIES WHICH HAVE BEEN PRESENTED AT THE NEW YORK ACADEMY OF MEDICINE FOR THE PAST 26 YEARS WILL BE DISCONTINUED.

BEGINNING IN NOVEMBER 1952, A SERIES OF

MONTHLY PANEL MEETINGS ON THERAPEUTICS FOR THE GENERAL PHYSICIAN

WILL BE PRESENTED. DATES, SUBJECTS AND PANEL MEMBERS WILL BE ANNOUNCED LATER.

NOTES ON THE HISTORY OF DIABETES MELLITUS*

Views Concerning Its Nature and Etiology up to the Discovery of the Role of the Pancreas

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IT IS WELL-KNOWN to every student of the history of medicine that Aretaeus of Cappadocia[1] speaks of diabetes as a disease characterized by emaciation and excessive urination. And he mentions that it had received its name (which means "a siphon") from the latter characteristic.

The observation of eastern physicians that the urine in diabetes tastes sweet seems to have remained unknown in the occident. The first mention in western medical literature of the "sapor mellitus" of diabetic urine is in Thomas Willis' *Practice of Physick*[2] which appeared in the second half of the 17th century. Willis, who was obviously much intrigued by his observation repeatedly speaks of the urine as being "exceedingly sweet" and as "wonderful sweet," but he in no manner ascribes this characteristic to the actual presence in it of sugar. In fact, he writes: ". . . it seems hard to demonstrate, why (it) is so wonderful sweet, or should taste like Honey; when rather . . . the flowing of the urin happens through the combination of salts, the liquor surely that were impregnated therewith should be saltish more than sweet. . . ."

Willis' observation was not generally confirmed. Some authors "on the contrary," writes Matthew Dobson,[3] a century later, "deny the existence of this quality, and consequently exclude it from being a characteristic of the disease." However, in his own experience, which extended to 9 cases, Dobson had always found the urine to be more or less sweet.

In chemical experiments on the urine of one of these patients Dobson demonstrated the presence of "a considerable quantity of saccharine

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matter," which, he felt, had not been formed in the kidney. Diabetes is, in his opinion a "species of imperfect digestion or assimilation," the sugar being a "product of the animal economy" or of the "digestive fermentation." In contrast to other authors who believed diabetes to be a disease of the liver or of the "secretory vessels of the kidney," he believes it to be "more a disease of the system in general." All of these views are expressed with great reserve.

Approaching the diabetes question from the pathologist's viewpoint, Matthew Baillie[4] stated, 20 years later, that "upon examination of the kidneys . . . it seemed probable that diabetes depends, in a considerable degree, upon a deranged action of the secretory structure of the kidneys, by which the blood there is disposed to new combinations," the effect of which is the production of "a saccharine matter." An alternate opinion which he, however, "proposed with much diffidence" was that "the chyle may be so imperfectly formed, as to make the blood be more readily changed into a saccharine matter, by the action of the kidneys."

In 1798, a year after the publication of Baillie's "Morbid Anatomy," there appeared the second edition of *Cases of the Diabetes Mellitus* by "John Rollo, M.D., Surgeon General of The Royal Artillery."[5] The Surgeon General, much less diffident, expressed his opinion with great assurance. "The Diabetes Mellitus," he writes, "is a disease of the stomach. . . . Its immediate cause . . . is a morbid condition (of this organ) forming or evolving from vegetable substances saccharine matter, which is quickly separated as a foreign body by the kidney."

Rollo who appears to have been a competent physician devised on the basis of his, as we now know, erroneous concepts of the nature of diabetes a regimen for its treatment which aimed at "preventing the formation of sugar, and diminishing the increased action of the stomach." This therapy consisted of ". . . confinement, an entire abstinence from every species of vegetable matter, a diet solely of animal food, with emetics, hepatised ammonia and narcotics. . . ." The "Rollo diet" which acquired great fame and was long used, was as follows: Breakfast: one and one-half pints of milk and a half pint of lime-water, mixed together; and bread and butter. Noon: Plain blood-puddings, made of blood and suet only. Dinner: Game, or old meats, which have been long kept; and as far as the stomach may bear, fat and rancid old meats, as pork. To eat in moderation. Supper: The same as breakfast.

This diet was first tried out on Captain Meredith, of the Royal

Artillery, of whom it has been said that he "shares some of his physician's fame, not unjustly, in view of what he went through."

It appears that diabetes was not too frequently encountered in those days, or possibly not too well recognized. Rollo, who was well acquainted with its symptoms and on the look out for it saw only two cases in a period of 19 years "although," as he says, he "had observed an extensive range of disease in America, the West Indies, and in England." Frank, the most famous German clinician of this period saw only three cases in twenty years, and Macintosh, in Edinburgh, mentions in his *Practice of Physic* that he had not seen a single case.

Although a number of theories concerning the nature of diabetes had been advanced, we find no mention of its possible etiology at the beginning of the 19th Century. This is understandable in view of its being so rarely encountered. During the next decades, however, when more cases were recognized, more attention was focused on the question of the exciting causes of this disease.

In his *Principles and Practice of Medicine* (1839) John Elliotson[6] speaks of "grief," "chills" and "excess of venery" as possible etiological factors. One of his patients who said that he had "never 'known a woman'" nevertheless died of diabetes. Which makes Elliotson believe that "it is very possible he had committed excess of a less creditable kind. I rather think this was the case, from the great length of the prepuce."

William Prout,[7] one of the outstanding diabetes specialists of those days, says that in his experience "exposure to cold"; "attacks of rheumatism and gout"; "the drinking of cold fluids while heated"; and "mental anxiety and distress" were the "most frequent exciting causes." In another connection Prout writes: "It is a remarkable fact, that Diabetes seems to be peculiar to mankind. . . . If such an immunity from Diabetes really exists among the inferior animals, its cause is very obscure." And then he makes the interesting comment: "Can the exemption be referred to that fertile cause of bodily disorder in human beings, the influence of mind?"

In contrast to Elliotson, who saw in diabetes a disease of the kidneys, Prout believed it to be a disease of the stomach predicated upon this organ's "morbidly active reducing" . . . and its "more or less suspended or paralyzed converting function." Nothing essential had been added to the concept of the nature of diabetes since the days of Dobson.

In the late 1840's it was an axiom that the animal organism received its sugar from extraneous sources and that these sources were always of vegetable origin. More specifically, the sugar encountered in animals stemmed, according to this view, from the sugar or starch contained in ingested vegetable material.

"In 1848 the physiological world," in the words of George Harley,[8] "seemed as if struck by a thunderbolt." The thunderbolt referred to was Claude Bernard's discovery that sugar production was a normal function also of the animal organism.

Bernard who had been working on nutrition and digestion for several years had been struck by the frequently made observation that the amount of sugar excreted by a diabetic often exceeded by far the amount consumed with his food. This could obviously not be reconciled with the prevailing view that all of the sugar encountered in the human organism was derived from ingested sugar or starch; nor was compatible with it the observation that a diabetic frequently excreted large amounts of sugar even when on a sugar-free diet. There was only one inference to be made from this, namely that the animal organism derives sugar also from sources other than ingested sugar or starch.

Since he visualized no method of investigating directly the mechanism of sugar *production*, in the animal organism, Bernard[9] decided to approach the problem indirectly. By following the course of ingested sugar to the point of its disappearance, i.e., to the point of its conversion into other products, one would be able (he believed) to determine what he called the "sugar assimilating organ." If it were then possible to "suppress" the action of this organ, thereby inducing a state of artificial diabetes, one would arrive at some kind of sugar production.

The results of Bernard's experiments are too well-known to need retelling. They did not disclose where introduced sugar disappears from the organism, but they revealed that sugar is formed even when sugar-free materials such as meat are ingested. This discovery indeed had the effect of a thunderbolt. It fundamentally altered the prevailing concepts of sugar metabolism and it moved the liver, the site of the newly discovered production of sugar, into the center of the diabetes problem. The liver became even more the pivot of this problem when Bernard[10] later published his discoveries concerning the mechanism by which glycogen is transformed into sugar through the action of a diastatic ferment.

"An entire revolution in the ideas of the physiology and pathology of diabetes" was effected, wrote Harley in 1866. These discoveries necessitated indeed a revision of the theory of diabetes and numerous authors advanced new concepts of the disease.

From today's vantage point we must say, however, that despite their brilliance and importance Bernard's discoveries did not bring closer the solution of the diabetes problem. Harley, who was a great admirer of Bernard's, formulated his theory of diabetes on the new knowledge. He ascribes an important place in it to the liver and he differentiates between two forms of diabetes: 1) from excessive formation of sugar; and 2) from defective assimilation of sugar. In the former, the normal stimulus of the liver is believed to be exaggerated resulting in an abnormally high "secretion" of this substance from the organ; and, writes Harley, "if the quantity formed be greater than the amount requisite to supply the wants of the system, the excess will be excreted with the urine and the disease diabetes mellitus established." As to the latter form, he argues: "the case may be reversed and there may still exist an abnormal amount of sugar in the blood, notwithstanding that only the proper amount has been secreted by the liver; this, of course, must of necessity happen when from any cause the process of assimilation has been interfered with and the body fails to consume its normal quantity of saccharine material."

And in this connection Harley speaks of Piorry's[11] suggestion to give, instead of withholding, sugar in diabetes and he comments that this form of therapy "may after all have more reason in it than at first sight appears. . . ."

Piorry had advocated the administration of sugar in diabetes on the assumption that in diabetics who had been long deprived of sugar or starch and who still continued to spill considerable amounts of sugar there would arise a need for this substance. "No one can doubt, indeed," he writes, "that this substance . . . is an essentially useful food; almost all animals strive to get it . . ., and, certainly, if the organism loses it through the urine, one must attempt to furnish it to the organism by way of the alimentary tract. Not because there is sugar in the urine do untoward events ("dès accidents," as he says) occur, but because the organ continuously loses and contains less of it."

Harley's views on diabetes are reflected in his comments on its therapy. Some authors, he writes, "may say, we want to stop the

elimination of the sugar. Not so; we want to stop the disease inducing it,—not the elimination of the sugar, which is the mere result of the disease. Retaining the sugar in the blood would only tend to hasten the death of the patient. . . . Remove the cause of the accumulation of saccharine matter in the blood if you can, but if you cannot do that, aid, instead of trying to retard, its elimination from the body."

There was, in his opinion, no single therapeutic approach to the disease. "I think," he writes, "if I were asked what is the best remedy for diabetes, I might venture to answer, in the language of Opie, when the student inquired what he mixed his colours with, 'Brains, Sir.' For to say that any one remedy or particular line of treatment is suitable to all cases of diabetes would be simply charlatanism of the worst sort."

Bernard's theory of glycogenolysis, despite its widespread acclaim, did not remain undisputed. Various authors, foremost among them, Frederick Pavy,[12] attempted to prove it incorrect. Pavy, who as a young man had worked in Bernard's laboratory, was convinced of the validity of Bernard's observations on glycogenolysis but disagreed strenuously with his interpretation of this phenomenon; and he spent many years of his long life in the attempt to disprove it. For Pavy glycogenolysis occurs only post-mortem and could, therefore, have no part in diabetes.

Distinguishing between two classes of the disease, Pavy postulated that in the one the "fault" lay simply in diminished "assimilative power over sugar." Barring this defect there is no difference between a diabetic and a healthy individual. In the other class there must evidently be something besides a defective assimilation of sugar since in these cases sugar appears in the urine even when all starchy food is excluded from the diet. And Pavy clearly places himself in the ranks of those who ascribed a dominant role to the liver in diabetes when he writes that the additional "something" is a "faulty action connected with the liver."

Claude Bernard himself, as one can readily understand, ascribed to the liver a central position in diabetes. According to his theory there occurs in this disease, for some unknown reason, increased "disassimilation," i.e., increased combustion of sugar in the liver. In an attempt to re-establish the disturbed equilibrium between assimilation and disassimilation, more glycogen is transformed into sugar which results in hyperglycemia and glycosuria and loss of sugar from the organism. In order to replace this loss the liver works at an increased pace: more

sugar is formed and ever more is excreted, until finally the organism is depleted thereof and fatal termination of the disease supervenes. The liver itself is not diseased in diabetes according to Bernard. On the contrary, he felt that "It sins through exuberant vitality."

He also repeatedly stressed that "it is not the nature of the material which is formed" in diabetes that spells the disease, but rather the existing disequilibrium between sugar formation and disintegration. And further: "The cause of diabetes . . . is more profound than the cause of the glycemia . . . which is merely the expression of a salutary physiological tendency. The real etiological element of the malady is the, at present, unknown cause of the primary organic weakness. . . ." "We should not attack the physiological symptoms of glycemia and glycosuria . . . but rather a more profound cause. . . ."

All of which was written as late as 1877,[13] more than a quarter of a century after the epochal discovery of the "Nouvelle Fonction du Foie." It clearly demonstrates that the "revolution" had not materially advanced the attack upon diabetes.

Although Bernard's work had greatly affected his contemporaries' views concerning the nature of diabetes, it had not added much to the concepts of its etiology. "Mental influences," "chilling," "drinking of cold beverages when overheated," "intemperance in eating and drinking," "sexual excesses" remained the main exciting causes. Further "hereditary disposition" was frequently supposed to play a role.

Bernard's discovery of artificial diabetes following "piqure" of the fourth ventricle[14] made many physicians feel that stimulation of the central or autonomic nervous systems could, on occasion, be an etiological factor. Dickinson,[15] in fact, defined diabetes as "a disease of the nervous system, characterized by the secretion of saccharine urine."

In 1884 there appeared a book on diabetes which has especial historical interest. In it von Frerichs,[16] towards the end of a distinguished medical career, summarizes the then existing knowledge of the disease and he comes to this conclusion: "The enigma of this sphinx will probably long remain unsolved and many a man will become its prey before its solution will be found." This gloomy view of the disease also found an expression in his poetic, but rather hard to translate, description of the diabetic: "He resembles a tired wanderer who, walking in a dense fog, along a narrow path on the banks of a roaring stream, is in constant danger of being therein engulfed. . . ." A few years earlier Dickin-

son had taken a less poetic but not less pessimistic view. Quoting Prout, who said that the diabetic "lives on the brink of a precipice," Dickinson continues: "Slight causes may suffice to loosen his feeble grip on life. He may quietly sink into the grave from want of the power to rally from small injury or trivial operation . . ., or even from the fatigue of a journey or some depression of mental origin. . . ." "If the diabetic patient by luck or pace has escaped the dangers of the road, he finds the end of his journey in incomplete or complete coma."

Work by many more authors than I have just reported on had been carried out in the forty years following Bernard's fundamental research. An entire revision of the concept of diabetes had taken place. However, the nature of this disease had not been clarified, its etiology had not been explained, its therapy had not been improved. The sphinx continued to lie in wait for its victims.

At the annual meeting of the "Versammlung deutscher Naturforscher & Aerzte," in 1889, Oskar Minkowski reported that total removal of the pancreas in dogs results in the picture of "real permanent diabetes mellitus, which corresponds in every detail to the most severe form of this disease in man."

The experiments which had culminated in this important discovery, and which represented the most outstanding contribution to the knowledge of diabetes since Claude Bernard's discovery of the glycogenic function of the liver, had not been undertaken with any intention of studying diabetes or even carbohydrate metabolism.[17] Since there are in circulation several incorrect versions of the origin of these experiments, it may be appropriate to quote Minkowski's own account.[18]

In 1928, forty years after their great discovery, Minkowski related in a lecture how he and von Mering happened to embark on the investigations which so unexpectedly led to the recognition of the role which the pancreas plays in diabetes. During a chance meeting, von Mering mentioned that while working on the resorption of fat, he had tried, unsuccessfully, to prevent the pancreatic juice from getting into the intestine by ligating the pancreatic duct. "Well, why don't you remove the pancreas?" countered Minkowski and, when von Mering answered that this would hardly be feasible, Minkowski, "in youthful audacity," glibly offered to try it. (He had a good deal of confidence in his surgical ability since he had successfully removed the liver in geese.) The same day the two men performed a total pancreatectomy in a dog. The

housebroken animal made a good recovery and postoperatively it was allowed to run around in the laboratory unrestrained. Coming into the laboratory one day Minkowski noticed that the dog had urinated on the floor. When he reproached the attendant for not having taken it into the yard on time, the "Diener" replied that he had done so; "but," he added, "the animal is very peculiar. Hardly has he emptied his bladder than he again voids large amounts of urine." An idea suddenly flashed through Minkowski's head. Taking a pipette he drew up a few cubic centimeters of the urine which had been voided onto the floor and tested it for sugar. The test was strongly positive!

We have arrived at another milestone in the history of diabetes. In consequence of the new discovery, the entire diabetes problem again underwent a revision. What followed does not fall into the scope of this presentation.

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TWENTY-FIFTH GRADUATE FORTNIGHT

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HORMONES IN HEALTH AND DISEASE

OCTOBER 6-17, 1952

Evening Lecture Program

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PRESIDENTIAL ADDRESS
Wm. Barclay Parsons

Ludwig Kast Award
HORMONES AND COMMON SENSE
Fuller Albright

HORMONES OF THE ANTERIOR PITUITARY GLAND
Abraham White

THE REGULATION OF WATER EXCRETION BY THE NEUROHYPOPHYSIS
H. B. van Dyke

Tuesday, October 7

CHEMISTRY OF THE STEROIDS
E. C. Kendall

DIAGNOSIS OF ENDOCRINE DISEASE: CLINICAL AND LABORATORY CONSIDERATIONS
Louis J. Soffer

Wednesday, October 8

THE ENDOCRINE CONTROL OF METABOLISM
Frank L. Engel

DISTURBANCES IN GROWTH
Lawson Wilkins

Thursday, October 9

MANAGEMENT OF ADDISON'S DISEASE IN ADRENALECTOMIZED PATIENTS
D. M. Bergenstal

ACTH, CORTISONE AND RELATED STEROIDS IN CLINICAL MEDICINE: PRACTICAL CONSIDERATIONS
Charles Ragan

Friday, October 10

PHEOCHROMOCYTOMA WITHIN AND WITHOUT THE ADRENAL MEDULLA
George F. Cahill

VIRILISM
Joseph W. Jailer

Monday, October 13

CUSHING'S SYNDROME
Abbie I. Knowlton

DIABETES: METABOLIC EFFECTS OF INSULIN
DeWitt Stetten, Jr.

Tuesday, October 14

THE PITUITARY THYROID RELATIONSHIP IN NORMAL AND DISORDERED THYROID STATES
Sidney C. Werner

CHOICE OF MANAGEMENT IN HYPERTHYROIDISM
Cyrus C. Sturgis

Wednesday, October 15

Carpenter Lecture
THYROIDITIS AND MYXEDEMA
David P. Barr

PARATHYROIDS AND CALCIUM METABOLISM
I. Snapper

Thursday, October 16

USE OF THE STEROIDS AND GONADOTROPINS IN GYNECOLOGY
Howard C. Taylor, Jr.

HORMONAL CONTROL OF NEOPLASTIC GROWTH
Rulon W. Rawson

Friday, October 17

THE RELATIONSHIP OF HORMONES TO PEPTIC ULCER
Joseph B. Kirsner

HORMONES AND THEIR INFLUENCE ON THE EMOTIONS
Francis J. Braceland

New York University-Bellevue Medical Center

SAMUEL ALBURTUS BROWN, M.D.

1874-1952

SAMUEL ALBURTUS BROWN, M.D.

1874 — 1952

Few men in our profession have had a more varied experience or filled more important positions than the late Dr. Samuel A. Brown. His whole career during sixty active years revolved around the New York University Medical School, and Bellevue Hospital. He received his M. D. degree in 1894 from the University when he was in his twentieth year, and his was the first class to graduate when the course had been lengthened from two to three years. He served on the Bellevue house staff two and a half years, twice the allotted period, because of changes on the attending staff. He was on the Second Division, and in the latter part of his tenure was on the gynecological service of Dr. William M. Polk his professor at the University and subsequently the first Dean of Cornell Medical College. Dr. Brown intended to become a gynecologist and for some time was an assistant to Dr. Polk. However, his own plans, and those of many others, were upset when all but four of the University medical faculty resigned to aid in the formation of the Cornell Medical College in 1897. A merger had been arranged between the New York University Medical College and the Bellevue Hospital Medical College, but this plan caused controversy and resulted in the formation of the Cornell enterprise. Dr. Brown chose to remain with the University group, and he became an assistant of Dr. Alfred L. Loomis together with Egbert Le Fevre and Warren Coleman. Le Fevre became Dean of the University and Bellevue union and succeeded the well-known Loomis as Professor of Medicine.

Dr. Brown often related to the writer that the financial backing given to Cornell was originally intended for the merged University and Bellevue project. This plan, however, failed when Dr. Loomis unexpectedly died while the formal arrangements were within a few days of completion. Lewis A. Stimson was professor of surgery during this period at the University and he was hostile to the merger with the Bellevue group, and he assumed a leading role in the formation and financing of the Cornell enterprise.

Dr. Brown began his teaching association with the University as an instructor in physical diagnosis, and he subsequently became Professor of Therapeutics. He was secretary of the University medical department when Le Fevre was dean and succeeded him in 1916 and acted in that capacity until 1932. When he retired from active teaching, the Samuel A. Brown Chair of Therapeutics was created in his honor, and he was given the titles of Emeritus Dean and Emeritus Professor. The honorary degree of Doctor of Public Health was accorded him by the University in 1926. He became president of the Society of the Bellevue Hospital Alumni in 1917, and in 1923 was elected president of the New York University College of Medicine Alumni Association. In 1932 he received the University Alumni Meritorious Service Award.

Dr. Brown was elected to Fellowship in the Academy in 1901. For more than twenty years he played an important part in the activities of the Academy. At various times, he served on the Committees on Admission, on Public Health Relations and on Medical Education. He was elected Vice-President in 1923 and President of the Academy in 1925. It was during his term as President that the present Academy building was completed and dedicated. Finally, he served as trustee from 1927 to 1936.

In his later years his main activity was the promotion of the New York University-Bellevue Medical Center, and to this ambitious project he devoted unceasing effort.

He had a prophetic vision that aided in bringing this worthy objective to the present stage of accomplishment. More than any other medical alumnus, he aroused the interest and enthusiasm of his friends and patients and eventually was responsible for many financial contributions to this important development in medical education and the care of the sick and injured. One of the honors he valued most was his position as Chairman and subsequently as Vice Chairman of the Board of Trustees of the Medical Center.

Dr. Brown had an extensive practice and an important group of patients, with many of whom he traveled to various parts of the continent and to far off places by land, sea and air. For twenty years he was Fleet Surgeon of the New York Yacht Club and thus became well known to a group of yachtsmen, many of whom would not go to sea without "Sam Brown" as their mentor and medical adviser and intimate friend. To them he became a legendary companion, and he was able to recruit their aid in any worthwhile project in which he was interested. Thus he was able to gain their support in the Medical Center enterprise to which he was devoted and for which he tirelessly gave his time and energy. He had the happy faculty of inspiring and imparting confidence and thus created a friendly relationship that lacked austerity or remoteness. As a medical consultant he was at his best in resolving difficulties and outlining a course to pursue in troublesome situations. During all his professional life he had been closely associated with a medical teaching institution and thus was known to thousands of young men who were preparing to enter the profession. After graduation these groups went afar throughout this country, to South America and abroad, and carried with them valued memories of their medical Alma Mater and of Dr. Brown, their Professor and Dean.

It is not well known that he was Lieutenant Colonel Brown of the 12th Regiment New York National Guard during the period 1903-1918, and then resigned as Brigade Surgeon and Brigade Quartermaster to enter the U. S. Army service in the Medical Reserve Corps.

He was a Consulting Physician in many hospitals, among them Bellevue, French, Polyclinic, Willard Parker, New Rochelle and Monmouth Memorial.

His wife, Charlotte Cowdrey Brown, died on March 6, 1941. She had been his valued aide and companion throughout his busy lifetime. The survivors in the family are two daughters, Mrs. D. Kenneth Rose and Mrs. Frederick T. Pierson, Jr., a brother, William P. Brown, and six grandchildren. Dr. Brown died suddenly of a recurrent heart attack March 16, 1952, while at the Hillsboro Club, Pompano, Florida.

And now he is among the elect of the Celestial City Clinic in the Great Beyond, joining his former confreres who aided in making our City a medical mecca. They will welcome him as one who rendered a great and lasting service and excelled in following the example they set in their own day and generation.

JOHN J. MOORHEAD

RECOMMENDATIONS ON MANUAL METHODS OF ARTIFICIAL RESPIRATION*

By the Committee on Public Health Relations

Intensive investigations during the past few years have indicated that the familiar Schafer prone pressure method of artificial respiration, which has been for many years taught and practiced in the United States, is considerably less efficient than some other methods of resuscitation. The recent announcement that the American Red Cross, the U. S. Department of Defense, the National Research Council, and the Public Health Service had officially recommended the Holger Nielsen, or back pressure-arm lift, method has awakened interest among all agencies concerned with life-saving techniques.

Acting on behalf of summer camp counsellors, the New York Tuberculosis and Health Association requested the advice of the Committee on Public Health Relations as to the desirability of recommending the Holger Nielsen technique to this group. A review of experimental studies under the auspices of the Council on Physical Medicine and Rehabilitation of the American Medical Association, the Red Cross and the Department of Defense, disclosed that of eight manual methods, three are more satisfactory than the others. These are designated as "push-pull" methods, as contrasted with others which consist of "pull" alone or "push" alone; that is, they produce both inspiration and expiration. The Schafer method produces only expiration and relies on the resiliency of the chest for inspiration; by careful measurements it has been shown to be only half as efficacious as the "push and pull" types of treatment.

The "push-pull" methods are described as follows:

1. *The hip lift-back pressure method*

This method supplements the old Schafer prone pressure method by adding the hip lift to produce inspiration. It alternates the lifting and lowering of the hips with pressure exerted on the lower part of the thorax. It is easy to learn and teach because it uses the same position for the operator as the Schafer method. The experimental studies showed that this method brought about the greatest pulmonary ventilation of any of those tested.

2. *The arm lift-back pressure method* (Holger Nielsen)

The victim is placed in the prone position with arms folded and hands placed one on the other. The face is then placed on the hands. The operator kneels at the victim's head and grasps the arms just above the elbows. The arms are drawn upward as the operator rocks backward until he meets firm resistance. The arms are replaced on the floor and the operator moves his hands to the midback (just below the scapulas) and rocks forward, exerting pressure to induce expiration. If the subject is large and the operator is small, this method may be substituted for the hip lift. Apparently it was selected for recommendation by the official agencies for general public use because of its simplicity for teaching and for performance, although it is slightly less efficient than the hip lift-back pressure.

3. *The arm lift-chest pressure method* (Silvester)

This method is satisfactory if the patient is on his back and for any reason must remain there. The arms are folded on the chest, and the operator kneels at the head. Grasping the arms just above the wrists, he draws them first upward, and then above the head until they touch the ground, inducing inspiration. The operator then places

* Prepared by a Subcommittee of which Dr. T. Campbell Thompson was chairman.

the arms again on the chest and presses downward to produce expiration.

Recommendations

After due consideration of all the circumstances, the Committee makes the following recommendations:

1. Because of the varied situations in which artificial respiration may be employed, the Committee is of the opinion that instruction in this life-saving measure should not be restricted to one method merely because it is easy for the operator to use.

2. All camp counsellors, first aid instructors, firemen, policemen and mine rescue crews should be familiar with the three push-pull methods outlined.

3. The method which provides the greatest possible respiratory exchange should be begun with the least possible delay. Neither ease of application nor fatigue of the operator should be considered during the crucial first five minutes. If the patient shows signs of life and cardiac function returns, a method requiring less effort may then be substituted if any further artificial respiration is needed.

References

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Back pressure-arm lift method for administering artificial respiration recommended. Report of the Council on Physical Medicine and Rehabilitation, *J. Amer. med. Assoc. 147*:1454-55, 1951.

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A LIST OF NEW BOOKS ADDED TO THE ACADEMY LIBRARY

The list of "Recent Accessions to the Library" which has hitherto been published in the *Bulletin of The New York Academy of Medicine* will cease to appear there hereafter. Instead, it will be issued in mimeographed form and will be available to Fellows of the Academy and to other libraries on request. Applications to be placed on its mailing-list should be made to the Librarian.

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AUTHORS	No. of Patients	Chronic, Resistant to Other Therapy	TYPES OF ULCERS				RELIEF OF SYMPTOMS (Chiefly Pain)				Surgery or Complications[1]	Side Effects Requiring Discontinuance of Drug[1]	EVIDENCE OF HEALING			
			Duodenal	Jejunal	Stomal	Gastric	Good	Fair	Poor	No Report			Complete	Moderate	None	No Report
Grimson, Lyons, Reeves	100	100	93	7			80	11	4		5		47		19	29
Friedman	15	15	14			1	5		4	6[2]			2		[3]	13
Bechgaard, Nielsen, Bang, Gruefund, Tobiassen	26	26	21			5	16	4	6				8	6	12	
McHardy, Browne, Edwards, Marek, Ward	162		162				136	12	11		3	1	14	9	7	129
Segal, Friedman, Watson	34	34	34[4]				14	13			7	2	5		8	14
Brown, Collins	117	99	117				97	7	8		5	8	55	9	8	40
Asher	77		65		7	5	52	9	16			16		9	21	47
Rodriguez de la Vega, Reyes Diaz	5	4	5				4		1					3	2	
Winkelstein	116	116	102	8		6	102		14				53		18	45
Hall, Hornicher, Weeks	18	18	18				11		1	6[5]			18			
Maier, Medi	38	38	24			14[6]	27	7	4[7]				10	2	5	21
Meyer, Jarmon	25	18	25				21		4							25
Poth, Fromm	37	37	37				33	3	1				33	3	1	
Plummer, Burke, Williams	41	41	41			[8]	36		5				38		3	
McDonough, O'Neil	104	100	104				63	10	31			11	4		11	89
Broders	60	60	58		1	1	35	19	6				10	1	49[9]	
Legerton, Teater, Ruffin	11		11				11									11
Holoubek, Holoubek, Langford	76	69	76				35	27	10		4	10	26		10	36
Ogburn	42		39	2		1	42[10]									42
Shanken	48	48	48				33	10	3		2		33	10	3	
Johnston	145	145	145				143		2			2	143		2	
Rossett, Knox, Stephenson	146		141			5	146					4[10]	53			93
TOTALS	1443	968	1380	17	8	38	1142	132	131	12	26	54	552	52	179	634
PERCENTAGES		67.8	95.6	1.2	0.6	2.6	81.3	9.4	9.3			3.7	70.5	6.6	22.9	

1. Not included in tabulations.
2. Included in "Relief of Symptoms" as "Poor" and in "Evidence of Healing" as "None."
3. Four had no symptoms when Banthine therapy was begun.
4. Of which seven were penetrative lesions and five partially obstructive.
5. No symptoms were present in four.
6. Two with symptoms only; no demonstrable ulcer.
7. Three were psychopathic patients and one had a ventricular ulcer of the lesser curvature.
8. Roentgen findings after treatment period of two weeks; forty-seven had duodenal deformity.
9. All returned to work within a week.
10. In these four, after relief of symptoms, Banthine was discontinued because of urinary retention.

During the past two years, more than 200 references to Banthine therapy in peptic ulcer and other parasympathotonic conditions have appeared in medical literature. Of these reports, 22 have presented specific facts and figures on the results of treatment in a total of 1,443 peptic ulcer patients, 67.8 per cent of whom were reported as chronic or resistant to other therapy. These results are tabulated above and show:

"Good" relief of symptoms was obtained in 81.3 per cent of the 1,405 patients on whom reports were available.

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In all but 9.7 per cent, relief of pain was "good" or "fair." In all but 22.9 per cent, evidence of healing was "complete" or "moderate."

During treatment, 26 patients required surgery or developed complications other than ulcer which required discontinuance of the drug before results could be evaluated.

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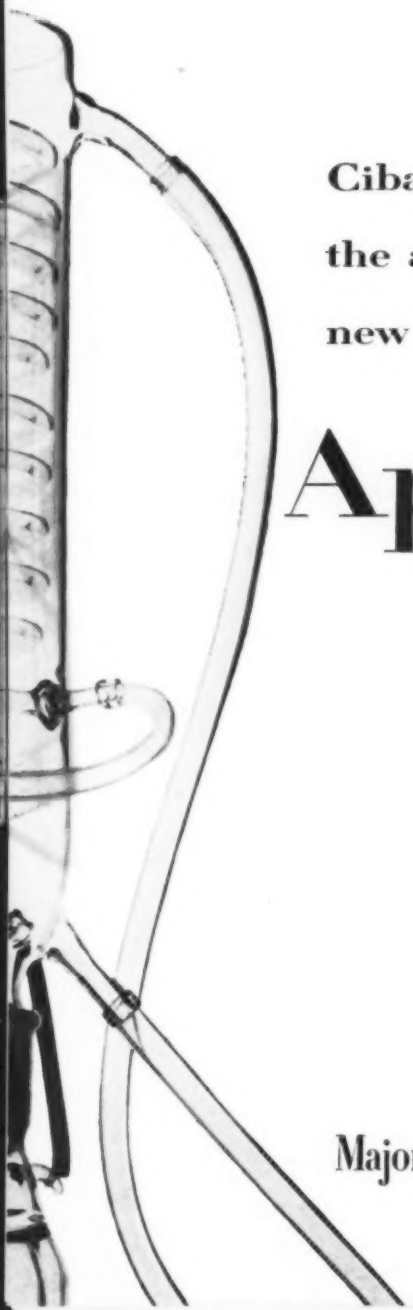

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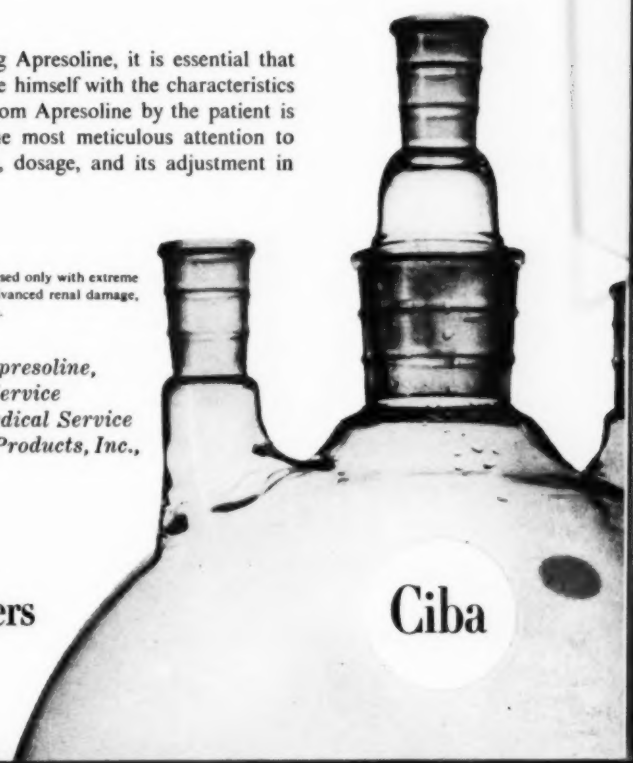

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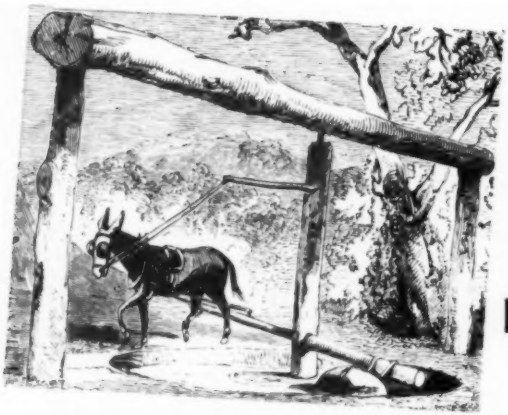

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2. Turell, R.: New York St. J.M. 50:2282, 1950.
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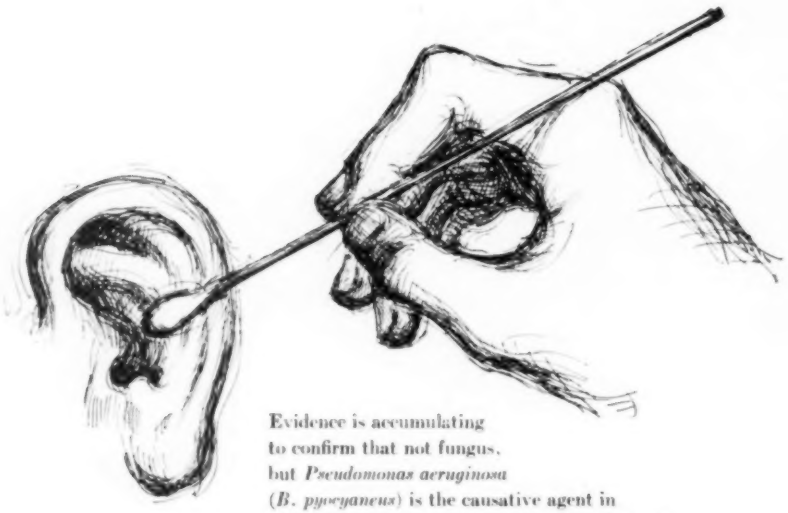

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1. Senturia, B. H.: Laryngoscope, 55:277, 1945.
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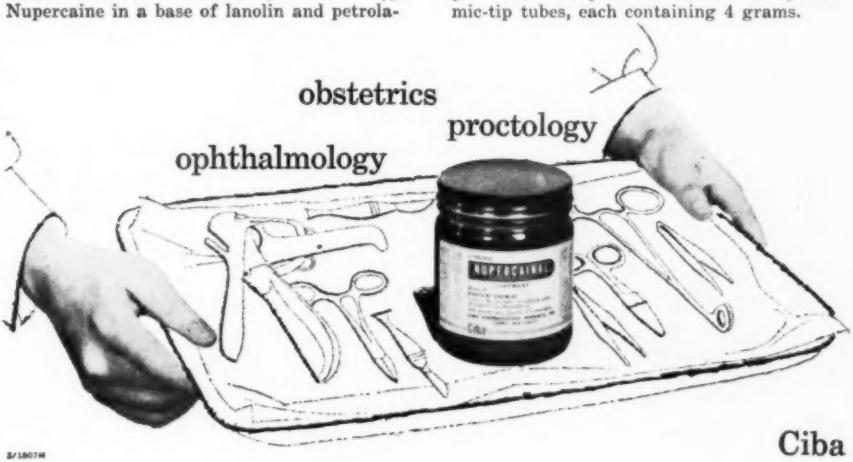

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JUNE 12—ENDOCRINE FACTORS IN HYPERTENSION—George A. Perera, *Associate Professor of Medicine, College of Physicians and Surgeons, Columbia University.*

JUNE 19—SYPHILIS AND PREGNANCY—Mortimer Speiser, *Associate Clinical Professor of Obstetrics and Gynecology, New York University College of Medicine.*

JUNE 26—RECENT ADVANCES IN THE SURGICAL MANAGEMENT OF PEPTIC ULCER—Ralph Colp, *Attending Surgeon, Mt. Sinai Hospital, Clinical Professor of Surgery, Columbia University.*

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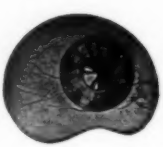

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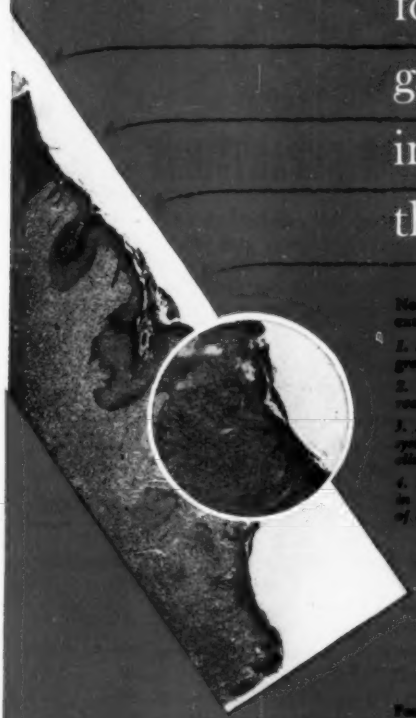

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1. Longacre, A. B.: P-92 Penicillin; Report of a Very Low Reaction Rate in Therapy with a New Penicillin Salt. Antibiotics & Chemotherapy 1:223 (July) 1951.
2. Kadison, E. R.; Ishihara, S. J., and Waters, T.: A New Form of Penicillin with Anti-Allergic Properties. Am. Pract. & Digest Treat. 2:411 (May) 1951.

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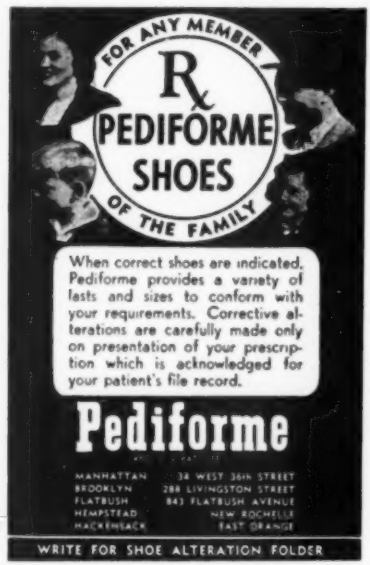
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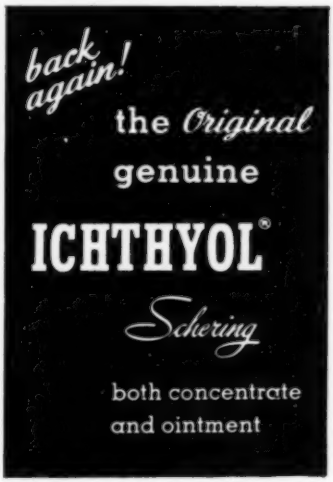

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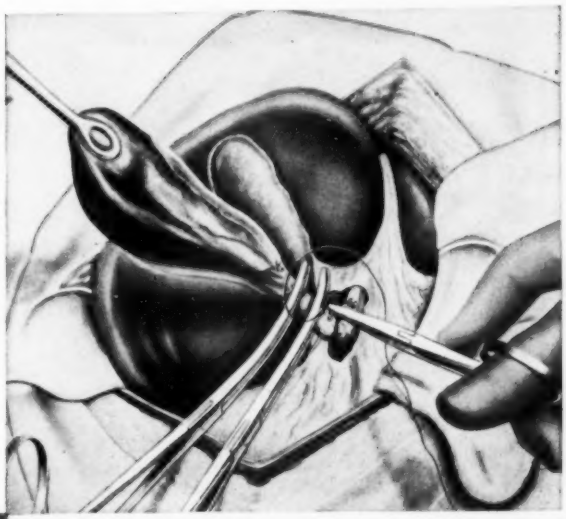

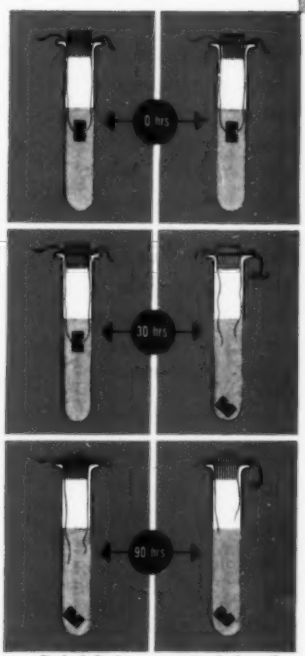

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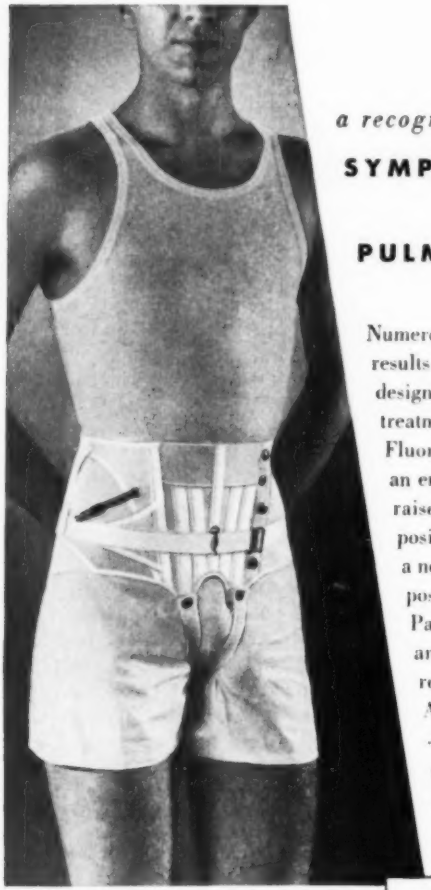

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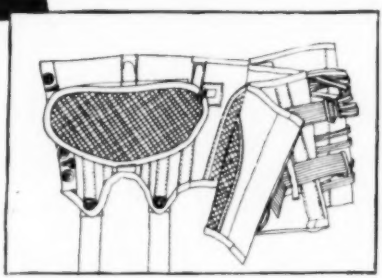

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1. Pulaski, E. J. and Connell, J. F., Jr.: Bull. U. S. Army M. Dept. 9:265.
2. Wooldridge, W. E. and Mast, G. W.: Am. J. Surg. 78:881.
3. Swalm, W. A.: M. Rec. 140:26.

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1. Greene, G. G.: Kentucky M. J. *50*:8, 1952.
2. Stevenson, C. S., et al.: Am. J. Obst. & Gynec. *61*:498, 1951.

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*Gordon, Harry H.: Feeding of Premature Infants, American Journal of Diseases of Children 73:713 (June) 1947.

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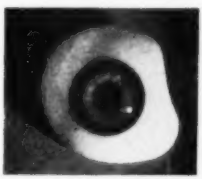

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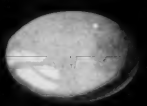

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1. Hazelton Laboratories, Falls Church, Va. Private communication.
2. Nesbit and Lapides. Univ. Michigan Med. Bull. 16, 37-42 (1950).
3. Richardson and Rose. J. Urol. 63, 1113-19 (1950).
4. Robbins, Colby, Sosman and Eyler, Radiology 56, 684-688 (1951).
5. Neuhaus, Christman and Lewis, J. Lab. Clin. Med. 35, 43-9 (1950).

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